PCT WORLD INTELLECTUA Interna

INTERNATIONAL APPLICATION PUBLISHED U

WO 9604274A1

(51) International Patent Classification 6 : C07D 403/14, 401/14, 405/14, 409/14, A61K 31/41 — A1

(11) International Publication Number: **WO 96/04274**

(43) International Publication Date: 15 February 1996 (15.02.96)

(21) International Application Number: PCT/GB95/01819

(22) International Filing Date: 1 August 1995 (01.08.95)

(30) Priority Data:

9415552.0	2 August 1994 (02.08.94)	GB
9415579.3	2 August 1994 (02.08.94)	GB
9426375.3	21 December 1994 (21.12.94)	GB

(71) Applicant *(for all designated States except US)*: MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BAKER, Raymond [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). BOURRAIN, Sylvie [FR/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). CASTRO PINEIRO, Jose, Luis [ES/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). CHAMBERS, Mark, Stuart [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). GUIBLIN, Alexander, Richard [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). HOBBS, Sarah, Christine [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). JELLEY, Richard, Alexander [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MADIN, Andrew [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MATASSA, Victor, Giulio [GB/IT]; Istituto Ricerche Di Biologia Molecolare, Via Pontina Km. 30,6000, I-00040 Pomezia (IT). REEVE, Austin, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). RUSSELL, Michael, Geoffrey, Neil [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SHOWELL, Graham, Andrew [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). STERNFELD, Francine [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). STREET, Leslie, Joseph [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). VAN NIEL, Monique, Bodil [NL/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: AZETIDINE, PYRROLIDINE AND PIPERIDINE DERIVATIVES

(57) Abstract

A class of substituted azetidine, pyrrolidine and piperidine derivatives are selective agonists of 5-HT_1-like receptors, being potent agonists of the human 5-$HT_{1D\alpha}$ receptor subtype whilst possessing at least a 10-fold selective affinity for the 5-$HT_{1D\alpha}$ receptor subtype relative to the 5-$HT_{1D\beta}$ subtype; they are therefore useful in the treatment and/or prevention of clinical conditions, in particular migraine and associated disorders, for which a subtype-selective agonist of 5-HT_{1D} receptors is indicated, whilst eliciting fewer side-effects, notably adverse cardiovascular events, than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

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AZETIDINE, PYRROLIDINE AND PIPERIDINE DERIVATIVES

The present invention relates to a class of substituted azetidine, pyrrolidine and piperidine derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT_1-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

It has been known for some time that 5-HT_1-like receptor agonists which exhibit selective vasoconstrictor activity are of use in the treatment of migraine (see, for example, A. Doenicke *et al.*, *The Lancet*, 1988, Vol. 1, 1309-11; and W. Feniuk and P.P.A. Humphrey, *Drug Development Research*, 1992, 26, 235-240).

The human 5-HT_1-like or 5-HT_{1D} receptor has recently been shown by molecular cloning techniques to exist in two distinct subtypes. These subtypes have been termed 5-$HT_{1D\alpha}$ (or 5-$HT_{1D\text{-}1}$) and 5-$HT_{1D\beta}$ (or 5-$HT_{1D\text{-}2}$), and their amino acid sequences are disclosed and claimed in WO-A-91/17174.

The 5-$HT_{1D\alpha}$ receptor subtype in humans is believed to reside on sensory terminals in the dura mater. Stimulation of the 5-$HT_{1D\alpha}$ subtype inhibits the release of inflammatory neuropeptides which are thought to contribute to the headache pain of migraine. The human 5-$HT_{1D\beta}$ receptor subtype, meanwhile, is located predominantly on the blood vessels and in the brain, and hence may play a part in mediating constriction of cerebral and coronary arteries, as well as CNS effects.

Administration of the prototypical 5-HT_{1D} agonist sumatriptan (GR43175) to humans is known to give rise at therapeutic doses to certain adverse cardiovascular events (see, for example, F. Willett *et al.*, *Br. Med. J.*, 1992, 304, 1415; J.P. Ottervanger *et al.*, *The Lancet*, 1993, 341, 861-2; and D.N. Bateman, *The Lancet*, 1993, 341, 221-4). Since sumatriptan barely discriminates between the human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptor subtypes (cf. WO-A-91/17174, Table 1), and since it is the blood vessels

with which the 5-$HT_{1D\beta}$ subtype is most closely associated, it is believed that the cardiovascular side-effects observed with sumatriptan can be attributed to stimulation of the 5-$HT_{1D\beta}$ receptor subtype. It is accordingly considered (cf. G.W. Rebeck *et al., Proc. Natl. Acad. Sci. USA*, 1994, 91, 3666-9) that compounds which can interact selectively with the 5-$HT_{1D\alpha}$ receptor subtype, whilst having a less pronounced action at the 5-$HT_{1D\beta}$ subtype, might be free from, or at any rate less prone to, the undesirable cardiovascular and other side-effects associated with non-subtype-selective 5-HT_{1D} receptor agonists, whilst at the same time maintaining a beneficial level of anti-migraine activity.

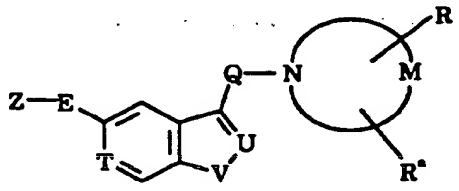
The compounds of the present invention, being selective 5-HT_1-like receptor agonists, are accordingly of benefit in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine. In particular, the compounds according to this invention are potent agonists of the human 5-$HT_{1D\alpha}$ receptor subtype. Moreover, the compounds in accordance with this invention have been found to possess at least a 10-fold selective affinity for the 5-$HT_{1D\alpha}$ receptor subtype relative to the 5-$HT_{1D\beta}$ subtype, and they can therefore be expected to manifest fewer side-effects than those associated with non-subtype-selective 5-HT_{1D} receptor agonists.

Several distinct classes of substituted five-membered heteroaromatic compounds are described in published European patent applications 0438230, 0494774 and 0497512, and published International patent applications 93/18029, 94/02477 and 94/03446. The compounds described therein are stated to be agonists of 5-HT_1-like receptors, and accordingly to be of particular use in the treatment of migraine and associated conditions. None of these publications, however, discloses nor even suggests the substituted azetidine, pyrrolidine and piperidine derivatives provided by the present invention.

Moreover, nowhere in the prior art available to date is there any disclosure of a subtype-selective 5-HT_{1D} receptor agonist having a 5-$HT_{1D\alpha}$ receptor binding affinity (IC_{50}) below 50 nM and at least a 10-fold selective affinity for the 5-$HT_{1D\alpha}$ receptor subtype relative to the 5-$HT_{1D\beta}$ subtype.

The compounds according to the present invention are subtype-selective 5-HT_{1D} receptor agonists having a human 5-$HT_{1D\alpha}$ receptor binding affinity (IC_{50}) below 50 nM, typically below 10 nM and preferably below 1 nM; and at least a 10-fold selective affinity, typically at least a 50-fold selective affinity and preferably at least a 100-fold selective affinity, for the human 5-$HT_{1D\alpha}$ receptor subtype relative to the 5-$HT_{1D\beta}$ subtype.

The present invention provides a compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;

T represents nitrogen or CH;

U represents nitrogen or C-R^2;

V represents oxygen, sulphur or N-R^3;

R^2 and R^3 independently represent hydrogen or C_{1-6} alkyl;

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

R represents a group of formula -W-R^1;

W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;

R^1 represents -OR^x, -SR^x, -SOR^x, -SO_2R^x or -NR^xR^y;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group; or R^x and R^y together represent a C_{2-6} alkylene group, which alkylene group may be optionally substituted by one or more substituents selected from C_{1-6} alkyl, aryl and hydroxy, or fused with a phenyl ring; and

R^a represents hydrogen, hydroxy, hydrocarbon or a heterocyclic group.

The present invention also provides compounds of formula I above wherein T represents CH; W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; R^1 represents -OR^x, -SR^x or -NR^xR^y; R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group; and Z, E, Q, U, V, M and R^a are as defined above.

The present invention further provides compounds of formula I above wherein Q represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms; T represents CH; W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; R^1 represents -OR^x, -SR^x or -NR^xR^y; R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group; R^a represents hydrogen; and Z, E, U, V and M are as defined above.

The present invention still further provides compounds of formula I above wherein Q represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms; T represents nitrogen; U represents C-R^2; V represents N-R^3; W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms; R^1 represents -OR^x, -SR^x or -NR^xR^y; R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group, or R^x and R^y together represent a C_{2-6} alkylene group; R^a represents hydrogen; and Z, E, R^2, R^3 and M are as defined above.

The five-membered heteroaromatic ring Z in the compounds of formula I above may be optionally substituted by one or, where possible, two substituents. As will be appreciated, where Z represents an oxadiazole, thiadiazole or tetrazole ring, only one substituent will be possible; otherwise, one or two optional substituents may be accommodated around the five-membered heteroaromatic ring Z. Examples of suitable substituents on the five-membered heteroaromatic ring Z include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano or trifluoromethyl.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable

pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, indanyl, aryl and aryl(C_{1-6})alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C_{3-7} heterocycloalkyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl and heteroaryl(C_{1-6})alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl, isobutyl, t-butyl and 2,2-dimethylpropyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Typical examples of C_{3-7} cycloalkyl(C_{1-6})alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

Particular indanyl groups include indan-1-yl and indan-2-yl.

Particular aryl groups include phenyl and naphthyl.

Particular aryl(C_{1-6})alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and morpholinyl groups.

Suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C_{1-6})alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridylmethyl, pyridylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolylmethyl and isoquinolylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, aminocarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, $-NR^vR^w$, $-NR^vCOR^w$, $-NR^vCO_2R^w$, $-NR^vSO_2R^w$, $-CH_2NR^vSO_2R^w$, $-NHCONR^vR^w$, $-CONR^vR^w$, $-SO_2NR^vR^w$ and $-CH_2SO_2NR^vR^w$, in which R^v and R^w independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl, or R^v and R^w together represent a C_{2-6} alkylene group.

When R^x and R^y, or R^v and R^w, together represent a C_{2-6} alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

When R^x and R^y together represent a C_{2-6} alkylene group, this group may be unsubstituted or substituted by one or more substituents selected from C_{1-6} alkyl, aryl and hydroxy. Typical substituents include methyl, phenyl and hydroxy.

Furthermore, when R^x and R^y together represent a C_{2-6} alkylene group, this group may optionally be fused with a phenyl ring. In this context, a typical group of formula $-NR^xR^y$ as defined for the substituent R^1 is 1,2,3,4-tetrahydroisoquinolinyl.

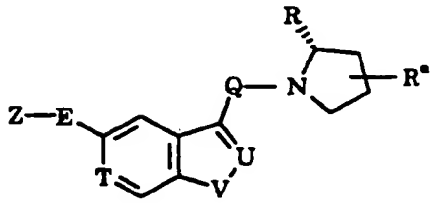
The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

The present invention includes within its scope prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible *in vivo* into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In particular, where M represents the residue of a pyrrolidine ring, and the substituent R is attached to the 2-position thereof, then the absolute stereochemical configuration of the carbon atom at the point of

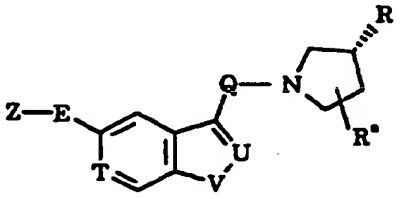
attachment of the moiety R is preferably as depicted in structure IA as follows:



(IA)

wherein Z, E, Q, T, U, V, R and R* are as defined above.

Moreover, where M represents the residue of a pyrrolidine ring, and the substituent R is attached to the 3-position thereof, then the absolute stereochemical configuration of the carbon atom at the point of attachment of the moiety R is preferably as depicted in structure IB as follows:



(IB)

wherein Z, E, Q, T, U, V, R and R* are as defined above.

The optionally substituted five-membered heteroaromatic ring Z in formula I is suitably a 1,3-oxazole, 1,3-thiazole, imidazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole or tetrazole ring. Preferably, the ring is a 1,3-oxazole, 1,3-thiazole, imidazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole or 1,2,4-triazole ring, in particular an imidazol-1-yl, 1,2,4-triazol-1-yl or 1,2,4-triazol-4-yl moiety.

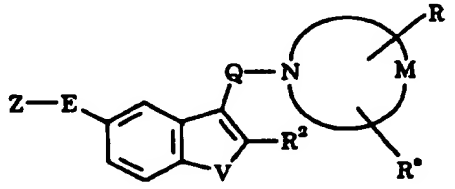
Suitably, the five-membered heteroaromatic ring Z is unsubstituted. Examples of optional substituents which may typically be attached to the moiety Z include methyl, ethyl, benzyl and amino.

Where E, Q and W, which may be the same or different, represent straight or branched alkylene chains, these may be, for example, methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or butylene. In addition, Q and W may be substituted in any position by a hydroxy group giving rise, for example, to a hydroxymethyl-methylene, 2-hydroxypropylene or 2-hydroxymethyl-propylene linkage. Moreover, E and W may each independently represent a chemical bond. Where E represents a chemical bond, the moiety Z is attached directly to the central fused bicyclic heteroaromatic ring system containing the variables T, U and V. Similarly, where W represents a chemical bond, the substituent R^1 is attached directly to the azetidine, pyrrolidine or piperidine ring of which M is the residue.

Suitably, E represents a chemical bond or a methylene linkage.

Suitably, Q represents an ethylene or propylene linkage.

The compound of formula I in accordance with the present invention is suitably an indole, benzofuran or benzthiophene derivative of formula IC, an indazole derivative of formula ID, or a pyrrolo[2,3-c]-pyridine derivative of formula IE:



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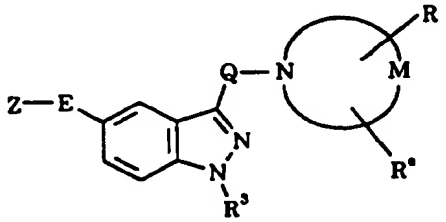

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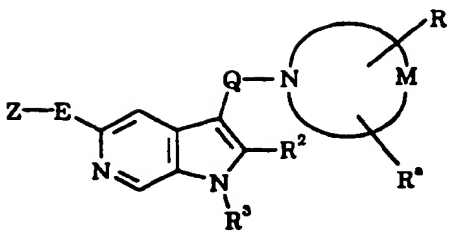
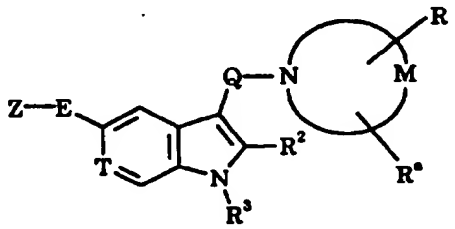


(IE)

wherein Z, E, Q, V, M, R, R^a, R^2 and R^3 are as defined above. Preferably, the compounds according to the invention are indole or pyrrolo[2,3-c]-pyridine derivatives of formula IF:



(IF)

wherein Z, E, Q, T, M, R, R^a, R^2 and R^3 are as defined above, in particular wherein R^2 and R^3 are both hydrogen.

Suitably, W represents a chemical bond or a methylene or hydroxymethyl-methylene linkage, in particular a chemical bond or a methylene linkage.

Suitably, R^x and R^y independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, indanyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted by one or more substituents selected typically from C_{1-6} alkyl, halogen, hydroxy, C_{1-6} alkoxy, aminocarbonyloxy, amino, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulphonylamino and C_{1-6} alkylaminosulphonylmethyl. Particular values of R^x and R^y include hydrogen, methyl, hydroxyethyl, isobutyl, 2,2-dimethylpropyl, allyl, dimethylallyl, 1-cyclohexylethyl, 2-cyclohexylethyl, indanyl, hydroxy-indanyl, phenyl, benzyl, methyl-benzyl, fluorobenzyl, methoxy-benzyl, acetylamino-benzyl, 1-phenylethyl, 2-phenylethyl, 2-hydroxy-1-

phenylethyl, 2-methoxy-1-phenylethyl, 2-aminocarbonyloxy-1-phenylethyl, 1-(fluorophenyl)ethyl, 1-(fluorophenyl)-2-hydroxyethyl, 1-(fluorophenyl)-2-methoxyethyl, 1-(acetylamino-phenyl)ethyl, 2-(acetylamino-phenyl)ethyl, 2-hydroxy-1-phenylprop-1-yl, 1-phenylprop-2-yl, 2-phenylprop-2-yl, 1-hydroxy-1-phenylprop-2-yl, 1-hydroxy-2-phenylprop-2-yl, 1-hydroxy-3-phenylprop-2-yl, furylmethyl, thienylmethyl and pyridylmethyl.

In addition, where R^x and R^y together represent an optionally substituted or phenyl ring-fused C_{2-6} alkylene group, the substituent $-NR^xR^y$ as defined for R^1 may suitably represent 3,3-dimethylpiperidinyl, 2-phenylpiperidinyl, 3-hydroxy-2-phenylpiperidinyl or 1,2,3,4-tetrahydroisoquinolin-2-yl.

Suitable values for the substituent R^1 include hydroxy, benzyloxy, methoxy-benzyloxy, pyridylmethoxy, benzylthio, fluorobenzyl-thio, phenylsulphinyl, benzylsulphinyl, fluorobenzyl-sulphinyl, fluorobenzyl-sulphonyl, amino, methylamino, indanylamino, hydroxyindanyl-amino, benzylamino, *N*-(methylbenzyl)-amino, *N*-(acetylamino-benzyl)-amino, *N*-(1-phenylethyl)-amino, *N*-(2-phenylethyl)-amino, *N*-(2-hydroxy-1-phenylethyl)-amino, *N*-(2-methoxy-1-phenylethyl)-amino, *N*-(2-aminocarbonyloxy-1-phenylethyl)-amino, *N*-[1-(fluorophenyl)ethyl]-amino, *N*-[1-(fluorophenyl)-2-hydroxyethyl]-amino, *N*-[1-(fluorophenyl)-2-methoxyethyl]-amino, *N*-[1-(acetylamino-phenyl)ethyl]-amino, *N*-[2-(acetylamino-phenyl)ethyl]-amino, *N*-(2-hydroxy-1-phenylprop-1-yl)-amino, *N*-(1-phenylprop-2-yl)-amino, *N*-(2-phenylprop-2-yl)-amino, *N*-(1-hydroxy-1-phenylprop-2-yl)-amino, *N*-(1-hydroxy-2-phenylprop-2-yl)-amino, *N*-(1-hydroxy-3-phenylprop-2-yl)-amino, *N*-(furylmethyl)-amino, *N*-(pyridylmethyl)-amino, dimethylamino, *N*-isobutyl-*N*-methylamino, *N*-(2,2-dimethylpropyl)-*N*-methylamino, *N*-allyl-*N*-methylamino, *N*-(3,3-dimethylprop-2-en-1-yl)-*N*-methylamino, *N*-(1-cyclohexylethyl)-*N*-methylamino, *N*-benzyl-*N*-methylamino, *N*-methyl-*N*-(methylbenzyl)-

amino, *N*-(fluorobenzyl)-*N*-methylamino, *N*-(acetylamino-benzyl)-*N*-methylamino, *N*-methyl-*N*-(1-phenylethyl)-amino, *N*-methyl-*N*-(2-phenylethyl)-amino, *N*-(2-hydroxy-1-phenylethyl)-*N*-methylamino, *N*-(2-methoxy-1-phenylethyl)-*N*-methylamino, *N*-[2-(acetylamino-phenyl)ethyl]-*N*-methylamino, *N*-(furylmethyl)-*N*-methylamino, *N*-methyl-*N*-(thienylmethyl)-amino, *N*-benzyl-*N*-(2-hydroxyethyl)-amino, *N*,*N*-bis(furylmethyl)-amino, 3,3-dimethylpiperidinyl, 2-phenylpiperidinyl, 3-hydroxy-2-phenylpiperidinyl and 1,2,3,4-tetrahydroisoquinolin-2-yl.

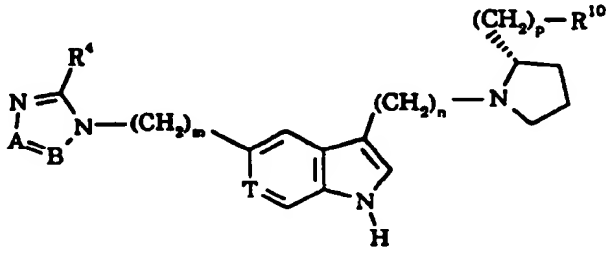
Particular values of the group R include hydroxy, benzyloxy, benzyloxymethyl, methoxy-benzyloxy, pyridylmethoxy, benzylthio-methyl, fluorobenzylthio-methyl, phenylsulphinylmethyl, benzylsulphinylmethyl, fluorobenzyl-sulphinyl, fluorobenzyl-sulphinylmethyl, fluorobenzyl-sulphonylmethyl, indanylamino, indanylaminomethyl, hydroxyindanyl-amino, benzylamino, benzylaminomethyl, 1-(*N*-benzylamino)-2-hydroxyethyl, *N*-(methylbenzyl)-aminomethyl, *N*-(acetylamino-benzyl)-amino, *N*-(acetylamino-benzyl)-aminomethyl, *N*-(1-phenylethyl)-amino, *N*-(1-phenylethyl)-aminomethyl, *N*-(2-phenylethyl)-aminomethyl, *N*-(2-hydroxy-1-phenylethyl)-amino, *N*-(2-hydroxy-1-phenylethyl)-aminomethyl, *N*-(2-methoxy-1-phenylethyl)-amino, *N*-(2-aminocarbonyloxy-1-phenylethyl)-amino, *N*-[1-(fluorophenyl)ethyl]-amino, *N*-[1-(fluorophenyl)-2-hydroxyethyl]-amino, *N*-[1-(fluorophenyl)-2-methoxyethyl]-amino, *N*-[1-(acetylamino-phenyl)ethyl]-amino, *N*-[1-(acetylamino-phenyl)ethyl]-aminomethyl, *N*-[2-(acetylamino-phenyl)ethyl]-amino, *N*-(2-hydroxy-1-phenylprop-1-yl)-amino, *N*-(1-phenylprop-2-yl)-amino, *N*-(2-phenylprop-2-yl)-aminomethyl, *N*-(1-hydroxy-1-phenylprop-2-yl)-amino, *N*-(1-hydroxy-2-phenylprop-2-yl)-amino, *N*-(1-hydroxy-3-phenylprop-2-yl)-amino, *N*-(furylmethyl)-amino, *N*-(furylmethyl)-aminomethyl, *N*-(pyridylmethyl)-aminomethyl, *N*-isobutyl-*N*-methyl-aminomethyl, *N*-(2,2-dimethylpropyl)-*N*-methyl-aminomethyl, *N*-allyl-*N*-methylamino, *N*-(3,3-dimethylprop-2-en-1-yl)-*N*-methylamino,

N-(1-cyclohexylethyl)-*N*-methyl-aminomethyl, *N*-benzyl-*N*-methylamino, *N*-benzyl-*N*-methyl-aminomethyl, *N*-methyl-*N*-(methylbenzyl)-aminomethyl, *N*-(fluorobenzyl)-*N*-methylamino, *N*-(acetylamino-benzyl)-*N*-methyl-aminomethyl, *N*-methyl-*N*-(1-phenylethyl)-aminomethyl, *N*-methyl-*N*-(2-phenylethyl)-aminomethyl, *N*-(2-hydroxy-1-phenylethyl)-*N*-methylamino, *N*-(2-hydroxy-1-phenylethyl)-*N*-methyl-aminomethyl, *N*-(2-methoxy-1-phenylethyl)-*N*-methylamino, *N*-[2-(acetylamino-phenyl)ethyl]-*N*-methylamino, *N*-(furylmethyl)-*N*-methylamino, *N*-methyl-*N*-(thienylmethyl)-amino, *N*-benzyl-*N*-(2-hydroxyethyl-aminomethyl, *N*,*N*-bis(furylmethyl)-amino, 3,3-dimethylpiperidinylmethyl, 2-phenylpiperidinyl, 2-phenylpiperidinylmethyl, 3-hydroxy-2-phenylpiperidinylmethyl and 1,2,3,4-tetrahydroisoquinolin-2-yl.

Suitable values of R^a include hydrogen, hydroxy and benzyl, especially hydrogen.

Suitably, R^2 and R^3 independently represent hydrogen or methyl, especially hydrogen.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

m is zero, 1, 2 or 3, preferably zero or 1;

n is 2, 3 or 4, preferably 2 or 3;

p is zero, 1 or 2;

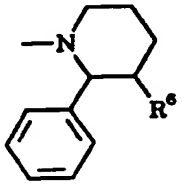
T represents nitrogen or CH;

A represents nitrogen or CH;

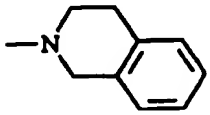
B represents nitrogen or C-R^5;

R^4 and R^5 independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano or trifluoromethyl; and

R^{10} represents -X-R^{11} or a group of formula (a) or (b):



(a)



(b)

in which

R^6 represents hydrogen or hydroxy;

X represents oxygen, sulphur, -SO-, -SO_2- or N-R^{12}; and

R^{11} and R^{12} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, indanyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

Examples of suitable optional substituents on the groups R^{11} and R^{12} include C_{1-6} alkyl, halogen, cyano, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aminocarbonyloxy, C_{2-6} alkylcarbonyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{2-6} alkylcarbonylamino, C_{1-6} alkylsulphonylamino and C_{1-6} alkylaminosulphonylmethyl.

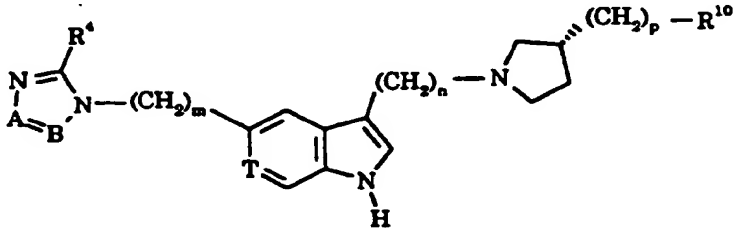
Particular values of R^4 and R^5 include hydrogen, methyl, ethyl, benzyl and amino, especially hydrogen.

Particular values of R^{11} and R^{12} include hydrogen, methyl, hydroxyethyl, isobutyl, 2,2-dimethylpropyl, allyl, dimethylallyl, 1-cyclohexylethyl, 2-cyclohexylethyl, indanyl, hydroxy-indanyl, phenyl, benzyl, methyl-benzyl, fluorobenzyl, methoxy-benzyl, acetylamino-benzyl,

1-phenylethyl, 2-phenylethyl, 2-hydroxy-1-phenylethyl, 2-methoxy-1-phenylethyl, 2-aminocarbonyloxy-1-phenylethyl, 1-(fluorophenyl)ethyl, 1-(fluorophenyl)-2-hydroxyethyl, 1-(fluorophenyl)-2-methoxyethyl, 1-(acetylamino-phenyl)ethyl, 2-(acetylamino-phenyl)ethyl, 2-hydroxy-1-phenylprop-1-yl, 1-phenylprop-2-yl, 2-phenylprop-2-yl, 1-hydroxy-1-phenylprop-2-yl, 1-hydroxy-2-phenylprop-2-yl, 1-hydroxy-3-phenylprop-2-yl, furylmethyl, thienylmethyl and pyridylmethyl.

In relation to formula IIA, the variable p is preferably 1.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:

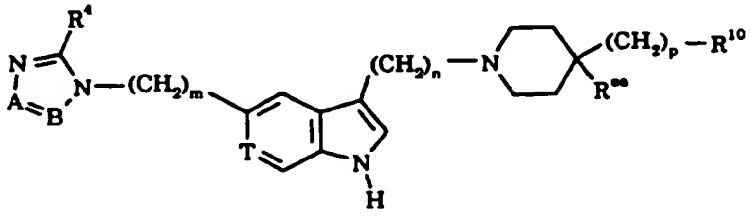


(IIB)

wherein m, n, p, T, A, B, R^4 and R^{10} are as defined with reference to formula IIA above.

In relation to formula IIB, the variable p is suitably zero or 1.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



(IIC)

wherein

R^{aa} represents hydrogen, hydroxy or aryl(C_{1-6})alkyl; and

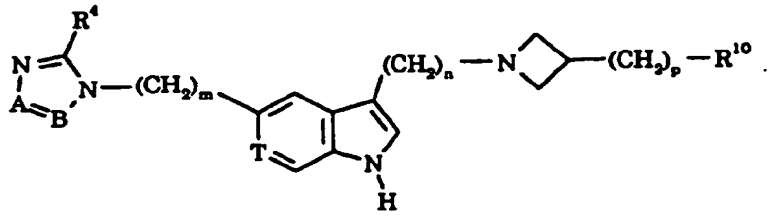
m, n, p, T, A, B, R^4 and R^{10} are as defined with reference to formula IIA above.

Suitable values of R^{aa} include hydrogen, hydroxy and benzyl, especially hydrogen.

In relation to formula IIC, the variable p is suitably zero or 1.

In one subset of the compounds of formula IIC above, R^{aa} is hydrogen.

A still further sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:



(IID)

wherein m, n, p, T, A, B, R^4 and R^{10} are as defined with reference to formula IIA above.

In relation to formula IID, the variable p is suitably zero or 1.

The present invention also provides compounds of formula IIA, IIB, IIC and IID as defined above wherein T represents CH; R^{10} represents -X-R^{11}; X represents oxygen, sulphur or N-R^{12}; R^{11} and R^{12} independently represent hydrogen, C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; and m, n, p, A, B and R^4 are as defined above.

The present invention further provides compounds of formula IIA, IIB and IIC as defined above wherein T represents nitrogen; R^{10} represents -X-R^{11}; X represents oxygen, sulphur or N-R^{12}; R^{11} and R^{12} independently represent hydrogen, C_{1-6} alkyl, aryl, aryl(C_{1-6})alkyl,

heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted; R^{aa} represents hydrogen; and m, n, p, A, B and R^4 are as defined above.

Specific compounds within the scope of the present invention include:

(3*R*)-3-benzyloxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(4-methoxyphenyl)methoxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(pyridin-3-yl)methoxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-benzyloxymethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(2*S*)-2-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

4-(4-acetylaminophenyl)methylamino-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-benzylamino-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(*N*-benzyl-*N*-methyl)amino-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(*N*-benzyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

(2*S*)-2-(*N*-benzyl-*N*-methylaminomethyl)-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-c]pyridin-3-yl)ethyl]pyrrolidine;

4-(*N*-benzyl-*N*-methyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-α-(methyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-(1-hydroxymethyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*S*)-(2-hydroxy-1-methyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*S*,2*R*)-(2-hydroxy-1-methyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*R*)-(2-hydroxy-1-methyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-acetylaminophenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methyl)benzylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-α-(methyl)benzylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-1-(4-acetylaminophenyl)ethylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-(4-acetylaminophenyl)ethylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-[(*R*)-α-(hydroxymethyl)benzyl]-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-[(*S*)-α-(hydroxymethyl)benzyl]-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(2-(4-acetylaminophenyl)ethyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(4-acetylaminobenzyl)-*N*-methylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(thien-2-yl)methyl-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]methylpiperidine;

(3*S*)-3-(4-acetylaminobenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(pyridin-4-ylmethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]azetidine;

4-benzyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

3-(*N*-benzyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]azetidine;

4-(*N*-benzyl)aminomethyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(*N*-benzyl-*N*-methyl)aminomethyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]azetidine;

(3*S*)-3-[*N*-(*R*)-α-(methyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-(methyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(furan-3-ylmethyl)amino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(furan-2-ylmethyl)amino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*R*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-benzyl-*N*-(2-hydroxy)ethyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(2-phenylethyl)amino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(2-phenylethyl)-*N*-methylamino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-α-dimethylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-methylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*R*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-methylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*R*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(imidazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[*N*-methyl-*N*-(*S*)-α-methylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[*N*-methyl-*N*-(*R*)-α-hydroxymethylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[*N*-methyl-*N*-(*S*)-α-methylcyclohexylmethyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[3-(*R*)-hydroxy-2-(*R*)-phenylpiperidin-1-yl]methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[3-(*R*)-hydroxy-2-(*R*)-phenylpiperidin-1-yl]methyl-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

4-hydroxy-4-(phenylsulfinyl)methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

(3*R*)-3-[2-(*R*,*S*)-phenylpiperidin-1-yl]methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

4-(3,3-dimethylpiperidin-1-yl)methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(*N*-isobutyl-*N*-methyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-[*N*-benzyl-*N*-(2-hydroxyethyl)amino]methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-[*N*-(2,2-dimethylpropyl)-*N*-methylamino]methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-[*N*-(*R*)-α-hydroxymethylbenzyl-*N*-methylamino]methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(2-pyridylmethyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(2-methylphenylmethyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-[*N*-(2-methylphenylmethyl)-*N*-methylamino]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

3-(benzylamino)methyl-3-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]pyrrolidine;

3-(benzylamino)methyl-3-hydroxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(carbamoyloxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*S*)-2-hydroxy-1-phenylpropylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*R*)-2-hydroxy-1-phenylpropylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*,*S*)-1-hydroxy-2-phenylprop-2-ylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-2-hydroxy-1-(4-fluorophenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*R*)-2-hydroxyindan-1-ylamino)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*,*S*)-indan-1-ylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*,*S*)-1-(4-fluorophenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-phenylprop-2-ylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(thien-3-ylmethyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(furan-3-ylmethyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(furan-3-ylmethyl)aminopiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*,*N*-di-(furan-3-ylmethyl)amino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(3,3-dimethylallyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(*N*-allyl-*N*-methylamino)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(indan-1-ylaminomethyl)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(*R*)-α-(hydroxymethyl)benzyl-*N*-methylaminomethyl]piperidine;

(3*R*)-3-(benzylthio)methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(±)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(1-benzylamino-2-hydroxyethyl)piperidine;

1-[3-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methyl)benzylamino]piperidine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methoxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(*R*)-α-(methoxymethyl)benzyl-*N*-methylamino]piperidine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methoxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-(4-fluorophenyl)-2-methoxyethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[*N*-(4-fluorobenzyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2-phenylpiperidin-1-yl)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-(4-fluorophenyl)-2-methoxyethylamino]piperidine;

(3*R*)-3-(benzylsulfinyl)methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(4-fluorobenzylthio)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(4-fluorobenzylsulfinyl)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(4-fluorobenzylsulfonyl)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

4-(4-fluorobenzylsulfinyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

and salts and prodrugs thereof.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a

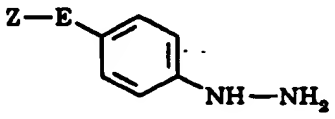
pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and

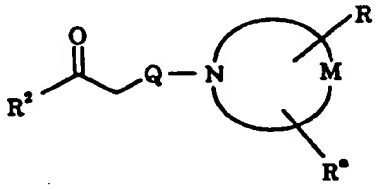
especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds according to the invention wherein T represents CH, U represents C-R^2 and V represents N-R^3, corresponding to the indole derivatives of formula IC as defined above, may be prepared by a process which comprises reacting a compound of formula III:



(III)

wherein Z and E are as defined above; with a compound of formula IV, or a carbonyl-protected form thereof:



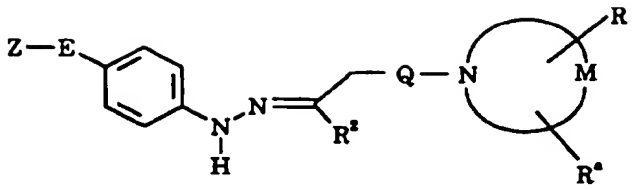
(IV)

wherein R^2, Q, M, R and R^a are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

The reaction between compounds III and IV, which is an example of the well-known Fischer indole synthesis, is suitably carried out by heating the reagents together under mildly acidic conditions, e.g. 4% sulphuric acid at reflux.

Suitable carbonyl-protected forms of the compounds of formula IV include the dimethyl acetal or ketal derivatives. Where the alkylene chain Q is substituted by a hydroxy group, this group may condense with the carbonyl moiety in compound IV whereby the carbonyl moiety is protected in the form of a cyclic hemiacetal.

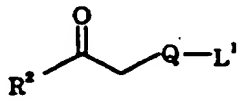
The Fischer reaction between compounds III and IV may be carried out in a single step, or may proceed via an initial non-cyclising step at a lower temperature to give an intermediate of formula V:



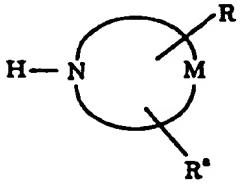
(V)

wherein Z, E, Q, R^2, M, and R^a are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

The intermediates of formula IV, or carbonyl-protected forms thereof, may be prepared by reacting a compound of formula VI, or a carbonyl-protected form thereof, with a compound of formula VII:



(VI)



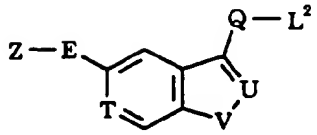
(VII)

wherein Q, R^2, M, R and R^a are as defined above, and L^1 represents a suitable leaving group.

The leaving group L^1 is suitably a halogen atom, e.g. chlorine or bromine.

Where L^1 represents a halogen atom, the reaction between compounds VI and VII is conveniently effected by stirring the reactants under basic conditions in a suitable solvent, for example sodium carbonate or potassium carbonate in 1,2-dimethoxyethane or *N,N*-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile, optionally in the presence of catalytic sodium iodide.

In an alternative procedure, the compounds according to the invention may be prepared by a process which comprises reacting a compound of formula VII as defined above with a compound of formula VIII:



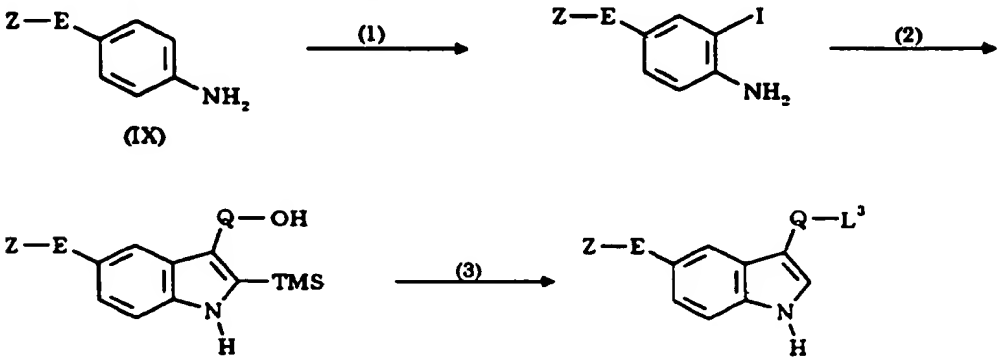
(VIII)

wherein Z, E, Q, T, U and V are as defined above, and L^2 represents a suitable leaving group.

The leaving group L^2 is suitably an alkylsulphonyloxy or arylsulphonyloxy group, e.g. methanesulphonyloxy (mesyloxy) or *p*-toluenesulphonyloxy (tosyloxy).

Where L^2 represents an alkylsulphonyloxy or arylsulphonyloxy group, the reaction between compounds VII and VIII is conveniently carried out in a suitable solvent such as isopropanol or 1,2-dimethoxyethane, typically in the presence of a base such as sodium carbonate or potassium carbonate, optionally in the presence of sodium iodide.

In one representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH and L^2 represents a mesyloxy or tosyloxy group may be prepared by the sequence of steps illustrated in the following reaction scheme (cf. Larock and Yum, *J. Am. Chem. Soc.*, 1991, 113, 6689):



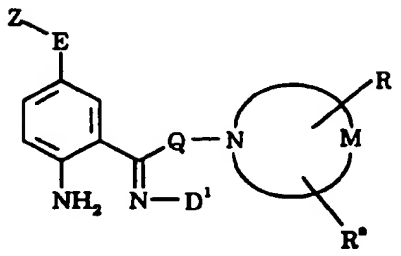
wherein Z, E and Q are as defined above, L^3 represents mesyloxy or tosyloxy, and TMS is an abbreviation for trimethylsilyl.

In Step 1 of the reaction scheme, the aniline derivative IX is treated with iodine monochloride, advantageously in methanol in the presence of a base such as calcium carbonate, in order to introduce an iodine atom *ortho* to the amine moiety. Step 2 involves a palladium-mediated coupling reaction with the protected acetylene derivative TMS-C≡C-Q-OH, typically using palladium acetate and triphenylphosphine in the presence of lithium chloride and sodium carbonate, suitably in *N,N*-dimethyl-formamide at an elevated temperature. This is followed in Step 3 by removal of the TMS moiety, ideally in refluxing methanolic hydrochloric acid; followed in turn by mesylation or tosylation, suitably by using mesyl chloride or tosyl chloride respectively in pyridine.

In another representative approach, the compounds of formula VIII wherein T and U both represent CH, V represents NH, Q represents a propylene chain and L^2 represents a mesyloxy or tosyloxy group may be prepared by reacting 3,4-dihydro-2*H*-pyran with a compound of formula III as defined above or a salt thereof, under a variant of the Fischer reaction conditions as described above for the reaction between compounds III and IV; followed by mesylation or tosylation of the 3-hydroxypropyl-indole derivative thereby obtained, typically by treatment with mesyl chloride or tosyl chloride under standard conditions.

The Fischer reaction with 3,4-dihydro-2*H*-pyran is suitably brought about by heating the hydrazine derivative III or an acid addition salt thereof, typically the hydrochloride salt, in an inert solvent such as dioxan, advantageously in the presence of a mineral acid such as hydrochloric acid or a Lewis acid such as zinc chloride, at the reflux temperature of the solvent.

In a further procedure, the compounds according to the invention wherein T represents CH, U represents nitrogen and V represents N-R^3, corresponding to the indazole derivatives of formula IB as defined above, may be prepared by a process which comprises cyclising a compound of formula X:

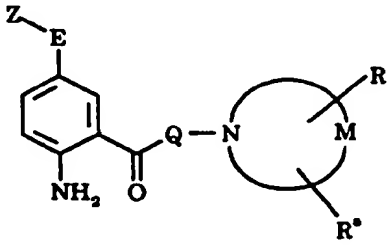


(X)

wherein Z, E, Q, M, R and R* are as defined above, and D^1 represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3.

The cyclisation of compound X is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of *m*-xylene and 2,6-lutidine at a temperature in the region of 140°C.

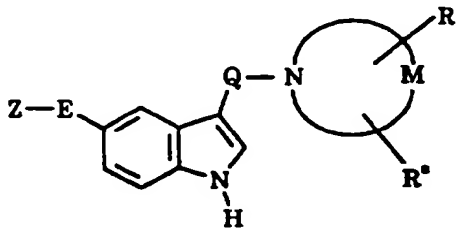
The readily displaceable group D^1 in the compounds of formula X suitably represents a C_{1-4} alkanoyloxy group, preferably acetoxy. Where D^1 represents acetoxy, the desired compound of formula X may be conveniently prepared by treating a carbonyl compound of formula XI:



(XI)

wherein Z, E, Q, M, R and R* are as defined above; or a protected derivative thereof, preferably the N-formyl protected derivative; with hydroxylamine hydrochloride, advantageously in pyridine at the reflux temperature of the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

The N-formyl protected derivatives of the intermediates of formula XI may conveniently be prepared by ozonolysis of the corresponding indole derivative of formula XII:

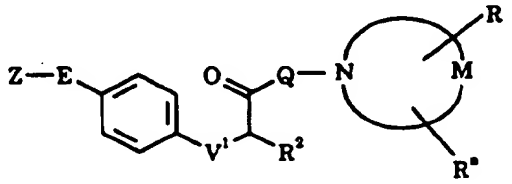


(XII)

wherein Z, E, Q, M, R and R^a are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

The indole derivatives of formula XII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

In a still further procedure, the compounds according to the invention wherein T represents CH, U represents C-R^2 and V represents oxygen or sulphur, corresponding to the benzofuran or benzthiophene derivatives of formula IA wherein V is oxygen or sulphur respectively, may be prepared by a process which comprises cyclising a compound of formula XIII:

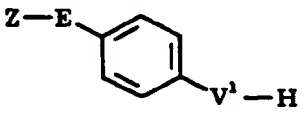


(XIII)

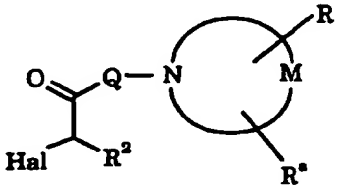
wherein Z, E, Q, R^2, M, R and R^a are as defined above, and V^1 represents oxygen or sulphur.

The cyclisation of compound XIII is conveniently effected by using polyphosphoric acid or a polyphosphate ester, advantageously at an elevated temperature.

The compounds of formula XIII may be prepared by reacting a compound of formula XIV with a compound of formula XV:



(XIV)



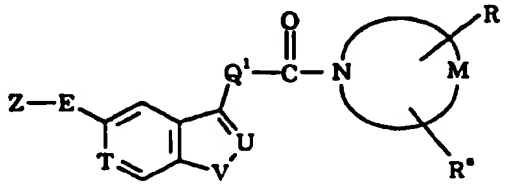
(XV)

wherein Z, E, Q, R^2, V^1, M, R and R^* are as defined above, and Hal represents a halogen atom.

The reaction is conveniently effected in the presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XIV may be prepared by a variety of methods which will be readily apparent to those skilled in the art. One such method is described in EP-A-0497512.

In a yet further procedure, the compounds according to the invention may be prepared by a process which comprises reducing a compound of formula XVI:



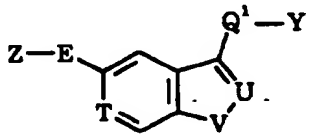
(XVI)

wherein Z, E, T, U, V, M, R and R^* are as defined above, and $-Q^1-CH_2-$ corresponds to the moiety Q as defined above.

The reaction is suitably carried out by treating the compound of formula XVI with a reducing agent such as lithium aluminium hydride in

an appropriate solvent, e.g. diethyl ether, tetrahydrofuran or mixtures thereof.

The compounds of formula XVI above may suitably be prepared by reacting a compound of formula VII as defined above with the appropriate compound of formula XVII:



(XVII)

wherein Z, E, T, U, V and Q^1 are as defined above, and Y represents a reactive carboxylate moiety.

Suitable values for the reactive carboxylate moiety Y include esters, for example C_{1-4} alkyl esters; acid anhydrides, for example mixed anhydrides with C_{1-4} alkanoic acids; acid halides, for example acid chlorides; and acylimidazoles.

By way of example, the intermediates of formula XVII above wherein Y is an acid chloride moiety may be prepared by treating the corresponding carboxylic acid derivative with thionyl chloride in toluene. Similarly, the intermediates of formula XVII wherein Y is an acylimidazole moiety may be prepared by treating the corresponding carboxylic acid derivative with 1,1'-carbonyldiimidazole. Alternatively, the reactive carboxylate moiety Y may be obtained by treating the corresponding compound wherein Y is carboxy with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate, optionally in the presence of triethylamine; the resulting activated carboxylate intermediate may then suitably be reacted *in situ* with the required compound of formula VII.

The hydrazine derivatives of formula III above may be prepared by methods analogous to those described in WO-A-94/02477, EP-A-0438230 and EP-A-0497512, as also may the aniline derivatives of formula IX.

Where they are not commercially available, the starting materials of formula VI, VII, XV and XVII may be prepared by the methods described in the accompanying Examples, or by analogous procedures which will be apparent to those skilled in the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I wherein R^x is benzyl initially obtained may be converted into a compound of formula I wherein R^x is hydrogen typically by conventional catalytic hydrogenation, or by transfer hydrogenation using a hydrogenation catalyst such as palladium on charcoal in the presence of a hydrogen donor such as ammonium formate. Moreover, a compound of formula I wherein R^1 is hydroxy initially obtained may be converted into the corresponding carbonyl compound (aldehyde or ketone) by treatment with a conventional oxidising agent such as sulphur trioxide-pyridine complex; the resulting carbonyl compound may then be converted in turn into a compound of formula I wherein R^1 represents $-NHR^y$, suitably by a standard reductive amination procedure which comprises treating the carbonyl compound with the appropriate amine of formula R^y-NH_2 in the presence of a suitable reducing agent, typically sodium cyanoborohydride. Alternatively, the carbonyl compound may be converted into a compound of formula I wherein R represents $-CH_2$-SOR^x and R^a represents hydroxy by treatment of the carbonyl compound with the anion of CH_3-SOR^x. Furthermore, a compound of formula I wherein R^1 represents $-NHR^y$ initially obtained may be converted into a further compound of formula I wherein R^1 represents $-NR^xR^y$, in which R^x corresponds to the group $-CH_2R^x$, suitably by a reductive amination procedure which comprises treating the compound of formula I wherein R^1 represents $-NHR^y$ with the appropriate aldehyde of formula R^x-CHO in the presence of a reducing agent such as sodium cyanoborohydride. In addition, a compound of

formula I wherein R^3 is hydrogen initially obtained may be converted into a compound of formula I wherein R^3 represents C_{1-6} alkyl by standard alkylation techniques, for example by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds in accordance with the present invention potently and selectively bind to the 5-$HT_{1D\alpha}$ receptor subtype, inhibit forskolin-

stimulated adenylyl cyclase activity, and stimulate [^{35}S]-GTPγS binding to membranes from clonal cell lines expressing human cloned receptors.

5-$HT_{1D\alpha}$/5-$HT_{1D\beta}$ Radioligand Binding

Chinese hamster ovary (CHO) clonal cell lines expressing the human 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors were harvested in PBS and homogenised in ice cold 50 mM Tris-HCl (pH 7.7 at room temperature) with a Kinematica polytron and centrifuged at 48,000g at 4°C for 11 min. The pellet was then resuspended in 50 mM Tris-HCl followed by a 10 min incubation at 37°C. Finally the tissue was recentrifuged at 48,000g, 4°C for 11 min and the pellet resuspended, in assay buffer (composition in mM: Tris-HCl 50, pargyline 0.01, $CaCl_2$ 4; ascorbate 0.1%; pH 7.7 at room temperature) to give the required volume immediately prior to use (0.2 mg protein/ml). Incubations were carried out for 30 min at 37°C in the presence of 0.02-150 nM [^{3}H]-5-HT for saturation studies or 2-5 nM [^{3}H]-5-HT for displacement studies. The final assay volume was 1 ml. 5-HT (10 μM) was used to define non-specific binding. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters (presoaked in 0.3% PEI/ 0.5% Triton X) followed by 2 x 4 ml washings with 50 mM Tris-HCl. The radioactive filters were then counted on a LKB beta or a Wallac beta plate counter. Binding parameters were determined by non-linear, least squares regression analysis using an iterative curve fitting routine, from which IC_{50} (the molar concentration of compound necessary to inhibit binding by 50%) values could be calculated for each test compound. The IC_{50} values for binding to the 5-$HT_{1D\alpha}$ receptor subtype obtained for the compounds of the accompanying Examples were below 50 nM in each case. Furthermore, the compounds of the accompanying Examples were all found to possess a selective affinity for the 5-$HT_{1D\alpha}$ receptor subtype of at least 10-fold relative to the 5-$HT_{1D\beta}$ subtype.

5-$HT_{1D\alpha}$/5-$HT_{1D\beta}$ Adenylyl Cyclase Assay

Studies were performed essentially as described in *J. Pharmacol. Exp. Ther.*, 1986, 238, 248. CHO clonal cell lines expressing the human cloned 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors were harvested in PBS and homogenised, using a motor driven teflon/glass homogeniser, in ice cold Tris HCl-EGTA buffer (composition in mM: Tris HCl 10, EGTA 1, pH 8.0 at room temperature) and incubated on ice for 30-60 min. The tissue was then centrifuged at 20,000g for 20 min at 4°C, the supernatant discarded and the pellet resuspended in Tris HCl-EDTA buffer (composition in mM: Tris HCl 50, EDTA 5, pH 7.6 at room temperature) just prior to assay. The adenylyl cyclase activity was determined by measuring the conversion of α-[^{33}P]-ATP to [^{33}P]-cyclic AMP. A 10 µl aliquot of the membrane suspension was incubated, for 10-15 min, in a final volume of 50 µl, at 30°C, with or without forskolin (10 µM), in the presence or absence of test compound. The incubation buffer consisted of 50 mM Tris HCl (pH 7.6 at room temperature), 100 mM NaCl, 30 µM GTP, 50 µM cyclic AMP, 1 mM dithiothreitol, 1 mM ATP, 5 mM $MgCl_2$, 1 mM EGTA, 1 mM 3-isobutyl-1-methylxanthine, 3.5 mM creatinine phosphate, 0.2 mg/ml creatine phosphokinase, 0.5-1 µCi α-[^{33}P]-ATP and 1 nCi [^{3}H]-cyclic AMP. The incubation was initiated by the addition of membrane, following a 5 min preincubation at 30°C, and was terminated by the addition of 100 µl SDS (composition in mM: sodium lauryl sulphate 2%, ATP 45, cyclic AMP 1.3, pH 7.5 at room temperature). The ATP and cyclic AMP were separated on a double column chromatography system (*Anal. Biochem.*, 1974, 58, 541). Functional parameters were determined using a least squares curve fitting programme ALLFIT (*Am. J. Physiol.*, 1978, 235, E97) from which E_{max} (maximal effect) and EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay,

the EC_{50} values for the 5-$HT_{1D\alpha}$ receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-$HT_{1D\alpha}$ receptor subtype relative to the 5-$HT_{1D\beta}$ subtype.

5-$HT_{1D\alpha}$/5-$HT_{1D\beta}$ GTPγS Binding

Studies were performed essentially as described in *Br. J. Pharmacol.*, 1993, 109, 1120. CHO clonal cell lines expressing the human cloned 5-$HT_{1D\alpha}$ and 5-$HT_{1D\beta}$ receptors were harvested in PBS and homogenised using a Kinematica polytron in ice cold 20 mM HEPES containing 10 mM EDTA, pH 7.4 at room temperature. The membranes were then centrifuged at 40,000g, 4°C for 15 min. The pellet was then resuspended in ice cold 20 mM HEPES containing 0.1 mM EDTA, pH 7.4 at room temperature and recentrifuged at 40,000g, 4°C for 15-25 minutes. The membranes were then resuspended in assay buffer (composition in mM: HEPES 20, NaCl 100, $MgCl_2$ 10, pargyline 0.01; ascorbate 0.1%; pH 7.4 at room temperature) at a concentration of 40 µg protein/ml for the 5-$HT_{1D\alpha}$ receptor transfected cells and 40-50 µg protein/ml for the 5-$HT_{1D\beta}$ receptor transfected cells. The membrane suspension was then incubated, in a volume of 1 ml, with GDP (100 µM for 5-$HT_{1D\alpha}$ receptor transfected cells, 30 µM for the 5-$HT_{1D\beta}$ receptor transfected cells) and test compound at 30°C for 20 min and then transferred to ice for a further 15 min. [^{35}S]-GTPγS was then added at a final concentration of 100 pM and the samples incubated for 30 min at 30°C. The reaction was initiated by the addition of membrane and was terminated by rapid filtration through Whatman GF/B filters and washed with 5 ml water. The radioactive filters were then counted on a LKB beta counter. Functional parameters were determined by a non-linear, least squares regression analysis using an iterative curve fitting routine, from which E_{max} (maximal effect) and

EC_{50} (the molar concentration of compound necessary to inhibit the maximal effect by 50%) values were obtained for each test compound. Of those compounds which were tested in this assay, the EC_{50} values for the 5-$HT_{1D\alpha}$ receptor obtained for the compounds of the accompanying Examples were below 500 nM in each case. Moreover, the compounds of the accompanying Examples which were tested were all found to possess at least a 10-fold selectivity for the 5-$HT_{1D\alpha}$ receptor subtype relative to the 5-$HT_{1D\beta}$ subtype.

EXAMPLE 1

(3R)-3-Benzyloxy-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. Hydrogen Oxalate. Hemihydrate.

1. Intermediate 1: 4′-(1,2,4-Triazol-4-yl)phenylhydrazine

a) 4′-Aminoacetanilide

A solution of 4-nitroacetanilide (5.0g, 27.8mmol) in EtOH/EtOAc (160ml, 1:1), H_2O (15ml) and 5N HCl (5.6ml, 28.0mmol) was hydrogenated over 10% Pd-C (0.50g) at 50 psi for 0.25h. The catalyst was removed by filtration through celite and the solvents removed under vacuum. The free base was generated by dissolving the product in H_2O, basifying with 2N NaOH and extracting into EtOAc. The combined extracts were dried ($MgSO_4$) and evaporated to give the title-*aniline* (3.75g, 90%). δ (250MHz, $CDCl_3$/d_4-MeOH) 2.10 (3H, s, Me), 6.68 (2H, d, J=8.8Hz, Ar-H), 7.27 (2H, d, J=8.8Hz, Ar-H).

b) 4′-(1,2,4-Triazol-4-yl)acetanilide

A mixture of the preceding aniline (3.52g, 23.4mmol), N,N-dimethylformamide azine (3.33g, 23.4mmol; *J. Chem Soc. (C)*, 1967, 1664) and p-toluenesulphonic acid monohydrate (0.223g, 1.17mmol), in

anhydrous toluene (100ml) was heated at reflux for 17h. The beige coloured precipitate was filtered off and washed with toluene and CH_2Cl_2 and dried under vacuum to give the desired triazole (4.29g, 91%), δ (250MHz, d_4-MeOH/d_6-DMSO) 2.14 (3H, s, CH_3), 7.60 (2H, d, J=8.8Hz, Ar-H), 7.78 (2H, d, J=8.8Hz, Ar-H), 8.96 (2H, s, Ar-H).

c) 4'-(1,2,4-Triazol-4-yl)aniline

A solution of the preceding acetamilide (4.91g, 24.3mmol) in 5N HCl (100ml) was heated at 125°C for 1.5h. The mixture was cooled to 0°C, basified with concentrated aqueous NaOH solution and extracted with CH_2Cl_2(x5). The combined extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1), to give the title-*aniline* (2.94g, 76%), δ (250MHz, $CDCl_3$) 3.80 (2H, s, NH_2), 6.71 (2H, d, J=8.8Hz, Ar-H), 7.08 (2H, d, J=8.8Hz, Ar-H), 8.36 (2H, s, Ar-H).

d) 4' (1,2,4-Triazol-4-yl)phenylhydrazine

To a solution of the preceding aniline (1.60g, 9.99mmol) in concentrated HCl/H_2O (23ml and 3ml respectively) was added, at -21°C, a solution of $NaNO_2$ (0.69g, 9.99mmol) in H_2O (8ml), at such a rate as to maintain the temperature below -10°C. The mixture was stirred for 0.3h and then filtered rapidly through a sinter, under vacuum. The filtrate was added to a cooled (-20°C) solution of $SnCl_2.2H_2O$ (9.02g, 40.0mmol) in concentrated HCl (17ml). The mixture was stirred at -20°C for 0.25h and then at room temperature for 1.25h. The resulting solid was filtered off, washed with Et_2O and dried under vacuum. The crude product was dissolved in H_2O, basified with concentrated aqueous NaOH and extracted with EtOAc (x5). The combined extracts were dried ($MgSO_4$) and evaporated to afford the title-product (0.95g, 54%), δ (250MHz, $CDCl_3$/d_4-MeOH) 3.98 (3H, br s, NH and NH_2), 6.97 (2H, d, J=12.0Hz, Ar-H), 7.25 (2H, d, J=12.0Hz, Ar-H), 8.48 (2H, s, Ar-H).

2. Intermediate 2: (3R)-4-(3-Benzyloxy)pyrrolidin-1-ylbutanal dimethylacetal

a) (3R)-N-*tert*-Butyloxycarbonylpyrrolidin-3-ol

A mixture of (3R)-N-benzylpyrrolidin-3-ol (Aldrich; 5.00g, 28.2mmol), di-*tert*-butyldicarbonate (7.39g, 33.8mmol), Pearlmans catalyst (0.55g), methanol (200ml) and water (20ml) were hydrogenated at 40psi in a Parr apparatus for 2h. The catalyst was removed by filtration through celite and the solvents removed under vacuum. The crude product was chromatographed on silica gel eluting with ethyl acetate/hexane (1:1) to give the title-pyrrolidinol (4.55g, 86%), δ (250MHz, $CDCl_3$) 1.46 (9H, s, $OC(Me)_3$), 1.87-2.03 (2H, m, CH_2), 2.07 (1H, s, OH), 3.33-3.50 (4H, m, 2 of CH_2), 4.42-4.48 (1H, m,C<u>H</u>-OH).

b) (3R)-N-*tert*-Butyloxycarbonyl-3-benzyloxypyrrolidine

A solution of (3R)-N-*tert*-butyloxycarbonylpyrrolidin-3-ol (2.25g, 12.0mmol), in anhydrous THF (10ml) was added portionwise to a slurry of sodium hydride (60% dispersion in oil, 0.63g, 13.8mmol) in THF (35ml) and the mixture stirred for 0.3h at 0°C. A solution of benzyl bromide (2.37g, 13.8mmol) in dry THF (2ml) was added and the mixture warmed to room temperature and stirred for 18h. Water (70ml) was added and the mixture extracted with ethyl acetate (3x100ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (100:0→97:3) to give the desired product (2.53g, 76%), δ (250MHz, $CDCl_3$) 1.46 (9H, s, $OC(Me)_3$), 1.87-2.11 (2H, m, CH_2), 3.42-3.50 (4H, m, 2 of CH_2), 4.10-4.16 (1H, m, C<u>H</u>-OBn), 4.53 (2H, s, $OC\underline{H}_2Ar$), 7.26-7.39 (5H, m, Ar).

c) (3R)-N-(H)-3-Benzyloxypyrrolidine

A solution of the preceding N-Boc pyrrolidine (5.0g, 18.0mmol) in 90% formic acid (150ml) was stirred at 0°C for 0.3h and then at room temperature for 2.5h. The solvents were removed under reduced pressure and the resulting residue was neutralised by addition of saturated K_2CO_3 solution. The aqueous was extracted with *n*-butanol (2 x 40ml), the solvent removed under vacuum and azeotroped with ethanol (x2). The product was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1) to give the title-product (2.62g, 82%), δ (250MHz, $CDCl_3$) 1.85-1.93 (2H, m, CH_2), 2.79-2.89 (2H, m, CH_2), 3.07-3.17 (2H, m, CH_2), 4.08-4.14 (1H, m, C<u>H</u>-OBn), 4.53 (2H, s, O<u>CH</u>$_2$Ar), 7.24-7.38 (5H, m, Ar-H).

d) (3R)-4-(3-Benzyloxy)pyrrolidin-1-ylbutanal dimethyl acetal

A mixture of 4-chlorobutanal dimethyl acetal (*J. Chem. Soc., Perkin Trans. 1*, 1981, 251-255; 2.29g, 15.0mmol), (3R)-N-(H)-3-benzyloxypyrrolidine (2.60g, 15.0mmol) and K_2CO_3 (2.23g, 16.0mmol), in dry THF (40ml), was heated at reflux for 48h. The mixture was cooled to room temperature, water (70ml) added and extracted with ethyl acetate (3 x 70ml). The combined extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel eluting with MeOH/CH_2Cl_2 (5:95) to give the title-dimethyl acetal (1.9g, 44%), δ (250MHz, $CDCl_3$) 1.57-1.67 (4H, m, 2 of CH_2), 1.84-1.96 (1H, m, CH of CH_2), 2.03-2.17 (1H, m, CH of CH_2), 2.46-2.74 (5H, m, 2 of CH_2 and CH of CH_2), 2.89 (1H, dd, J=10.3 and 6.1Hz, CH of CH_2), 3.31 (6H, s, CH(O<u>Me</u>)$_2$), 4.10-4.18 (1H, m, C<u>H</u>OBn), 4.38 (1H, t, J=5.2Hz, C<u>H</u>(OMe)$_2$), 4.48 (2H, ABq, J=11.9Hz, C<u>H</u>$_2$OAr), 7.24-7.38 (5H, m, Ar).

3. (3R)-3-Benzyloxy-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl] pyrrolidine, Hydrogen Oxalate, Hemihydrate.

A solution of Intermediate 1 (1.25g, 7.1mmol) and Intermediate 2 (1.90g, 6.48mmol) in 4% H_2SO_4 (25ml) was heated at reflux for 48h. The mixture was cooled to room temperature and basified with K_2CO_3. The product was extracted into ethyl acetate (x3), the combined extracts dried ($MgSO_4$) and the solvent removed under vacuum. The crude product was purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (90:8:1) to give the title-indole (0.55g, 22%). The hydrogen oxalate hemihydrate salt was prepared: mp 97-98°C. (Found: C, 61.76, H, 5.56, N, 14.28. $C_{23}H_{25}N_5O \cdot C_2H_2O_4 \cdot 0.5\ H_2O$ requires C, 61.72, H, 5.80, N, 14.39%), m/e 388 ($M+1^+$), δ (360MHz, D_6-DMSO) 1.96-2.22 (2H, m, CH_2), 3.02-3.28 (4H, m, 2 of CH_2), 4.24-4.28 (1H, m, C<u>H</u>-OBn), 4.50 (2H, s, C<u>H</u>$_2$Ar), 7.29-7.38 (7H, m, Ar-H), 7.51 (1H, d, J=8.6Hz, Ar-H), 7.87 (1H, d, J=1.8Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.25 (1H, s, NH).

EXAMPLE 2

(3R)-3-(4-Methoxybenzyloxy)-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl] pyrrolidine, 1.2 Oxalate, Hemihydrate.

1. Intermediate 3: 2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]ethyl alcohol

a) 2-Iodo-4-(1,2,4-triazol-4-yl)phenylaniline

A solution of iodine monochloride (22.3g, 137mmol) in methanol (300ml) was added over 0.75h to a stirred suspension of 4-(1,2,4-triazol-4-yl)phenylaniline (20.0g, 125mmol) and calcium carbonate (25.0g, 250mmol) in methanol (800ml) at -30°C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 16h before filtering through a pad of celite. The filtrate was evaporated *in vacuo* and the residue dissolved in EtOAc and washed with 50% w/w sodium bisulphite

solution. The solid material was filtered off and the organic layer dried ($MgSO_4$), evaporated *in vacuo* and combined with the solid material to give the title product (23.9g, 67%), δ (250MHz, d_6-DMSO) 5.54 (2H, br s, NH_2), 6.84 (1H, d, J=8.7Hz, Ar-H), 7.38 (1H, dd, J=2.6 and 8.7 Hz, Ar-H), 7.87 (1H, d, J=2.5Hz, Ar-H), 8.92 (2H, s, Ar-H).

b) 2-[5-(1,2,4-Triazol-4-yl)-2-trimethylsilyl-1H-indol-3-yl]ethyl alcohol

A mixture of the preceding iodoaniline (23.9g, 83.6mmol), 4-trimethylsilyl-3-butyn-1-ol (prepared by silylation of 3-butyn-1-ol) (17.83g, 125.3mmol), lithium chloride (3.54g, 83.6mmol), sodium carbonate (44.24g, 417.8mmol) and triphenylphosphine (1.10g, 4.18mmol) in DMF (900ml) was degassed with nitrogen for 0.5h at room temperature. Palladium (II) acetate (0.94g, 4.18mmol) was added in one portion and the mixture heated at 100°C under nitrogen for 6h. A second portion of palladium (II) acetate (5g, 22.2mmol) was added and the mixture heated at 100°C for 1h. The solvent was evaporated *in vacuo* and the residue partitioned between ethyl acetate (800ml) and water (1000ml) and filtered through celite. The aqueous layer was separated and re-extracted with ethyl acetate (3 x 800ml). The combined extracts were dried and evaporated, and the crude product chromatographed on silica gel, eluting with CH_2Cl_2/EtOH/NH_3 (80:8:1), to give the title product (8.5g, 34%), δ (250MHz, d_6-DMSO) 0.38 (9H, s, $SiMe_3$), 2.97 (2H, t, J=7.6Hz, CH_2), 3.58 (2H, m, CH_2), 4.69 (1H, t, J=5.3Hz, OH), 7.30 (1H, dd, J=2.1 and 8.6 Hz, Ar-H), 7.48 (1H, d, J=8.7Hz, Ar-H), 7.78 (1H, d, J=2.1Hz, Ar-H), 9.03 (2H, s, Ar-H), 10.83 (1H, br s, NH).

c) 2-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]ethyl alcohol

A solution of the preceding 2-trimethylsilyl-indole (8.5g, 28.3mmol) in methanol (68ml) and 5N HCl (57ml) was heated at 60°C for 16h. The methanol was evaporated *in vacuo* and the residue neutralised with concentrated NH_3 solution. The precipitate was filtered off, washed with

Et_2O (2x100ml) and dried *in vacuo* to give the title alcohol (6.0g, 92%), δ (250MHz, d_6-DMSO), 2.88 (2H, t, J=7.2Hz, CH_2), 3.68 (2H, m, CH_2), 4.66 (1H, br s, OH), 7.23-7.32 (2H, m, Ar-H), 7.48 (1H, d, J=8.5Hz, Ar-H), 7.81 (1H, d, J=2.1Hz, Ar-H), 9.03 (2H, s, Ar-H), 11.15 (1H, br s, NH).

2. Intermediate 4: (3R)-N-(H)-3-(4-Methoxybenzyloxy) pyrrolidine

a) (3R)-N-*tert*-Butyloxycarbonyl-3-(4-methoxybenzyloxy)pyrrolidine

A solution of (3R)-N-*tert*-butyloxycarbonylpyrrolidin-3-ol (2.00g, 10.7mmol) in anhydrous DMF (12ml) was added dropwise to a stirred slurry of sodium hydride (60% dispersion in oil, 0.465g, 11.6mmol) in DMF (25ml) at -10°C under nitrogen and the mixture stirred at this temperature for 0.67h. 4-Methoxybenzyl chloride (1.52ml, 11.2mmol) was added dropwise and the mixture warmed to 0°C over 1h and then stirred at RT for 2h. Water was added and the mixture poured into ether and washed with water (x3). The ethereal layer was dried ($MgSO_4$), evaporated *in vacuo* and the crude product chromatographed on silica gel, eluting with ethyl acetate/hexane (30:70), to afford the title pyrrolidine (3.09g, 94%), δ (250MHz, $CDCl_3$) 1.46 (9H, br s, $OC(Me)_3$), 1.73-2.09 (2H, m, CH_2), 3.40-3.46 (4H, m, 2 of CH_2), 3.81 (3H, s, OMe), 4.12 (1H, m, C<u>H</u>OCH_2Ar), 4.45 (2H, s, O<u>C</u>H_2Ar), 6.85-6.91 (2H, m, Ar-H), 7.23-7.27 (2H, m, Ar-H).

b) (3R)-N-(H)-3-(4-Methoxybenzyloxy)-pyrrolidine

Prepared from the preceding N-Boc pyrrolidine as described for Example 1, part 2c, δ (250MHz, $CDCl_3$) 1.85-1.93 (2H, m, CH_2), 2.81-2.91 (2H, m, CH_2), 3.06-3.17 (2H, m, CH_2), 3.80 (3H, s, OMe), 4.10 (1H, m, C<u>H</u>OCH_2Ar), 4.41 (2H, s, O<u>C</u>H_2Ar), 6.85-6.91 (2H, m, Ar-H), 7.23-7.27 (2H, m, Ar-H).

3. (3R)-3-(4-Methoxybenzyloxy)-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine, 1.2 Oxalate Hemihydrate.

Methanesulphonyl chloride (0.20ml, 2.62mmol) was added dropwise to a stirred suspension of Intermediate 3 (400mg, 1.75mmol) in pyridine (10ml) at -10°C under nitrogen. The mixture was warmed to, and stirred at, room temperature overnight and the solvent evaporated under high vacuum. The residue was partitioned between ethyl acetate and water and the aqueous layer extracted with ethyl acetate (x4). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue (335mg) was taken with sodium carbonate (161mg, 1.07mmol) and sodium iodide (114mg, 1.08mmol) in 1,2-dimethoxyethane (8ml) and a solution of Intermediate 4 (224mg, 1.08mmol) in 1,2-dimethoxyethane (2ml) added. The mixture was heated at reflux under nitrogen for 21h in the dark. Water was added and the mixture extracted with ethyl acetate (3 x 100ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*, and the residue chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (90:8:1), to give the title indole (87mg, 12%). The 1.2 oxalate hemihydrate salt was prepared. (Found: C, 59.47, H, 5.49, N, 12.99. $C_{24}H_{27}N_5O_2 \cdot 1.2(C_2H_2O_4) \cdot 0.5\ H_2O$ requires C, 59.32, H, 5.73, N, 13.10%), m/e ($M+1^+$) 418, δ (360MHz, d_6-DMSO) 2.06 (1H, m, CH of CH_2), 2.18 (1H, m, CH of CH_2), 3.07-3.11 (2H, m, CH_2), 3.20-3.42 (6H, m, 3 of CH_2), 3.74 (3H, s, OMe), 4.27 (1H, m, C<u>H</u>OCH_2Ar), 4.43 (2H, s, CHOC<u>H</u>$_2$Ar), 6.89 (2H, d, J=8.7Hz, 2 of Ar-H), 7.25 (2H, d, J=8.6Hz, 2 of Ar-H), 7.31 (1H, dd, J=2.1 and 8.4Hz, Ar-H), 7.35 (1H, s, Ar-H), 7.51 (1H, d, J=8.4Hz, Ar-H), 7.81 (1H, d, J=2.0Hz, Ar-H), 8.89 (2H, s, Ar-H), 11.08 (1H, br s, NH).

EXAMPLE 3

(3R)-3-(Pyridin-3-ylmethyloxy)-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. Bisoxalate. 0.25 Hydrate.

a) (3R)-N-*tert*-Butyloxycarbonyl-3-(pyridin-3-ylmethyloxy)pyrrolidine

A suspension of 3-picolylchloride hydrochloride (1.84g, 11.2mmol) in DMF (50ml) was added to a stirred slurry of sodium hydride (60% dispersion in oil, 0.45g, 11.2mmol) in DMF at 0°C under nitrogen. The mixture was stirred at 0°C for 0.25h and then added to a mixture of (3R)-N-*tert*-butyloxycarbonylpyrrolidin-3-ol (2.0g, 10.7mmol) and sodium hydride (60% dispersion in oil, 0.45g, 11.2mmol) in DMF at 0°C under nitrogen (mixture stirred for 0.2h at 0°C prior to the addition). The reaction mixture was stirred at room temperature for 2.5h. Water (200ml) was added and the mixture extracted with ethyl acetate (1 x 200ml), dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was chromatographed on silica gel, eluting with Et_2O/MeOH (95:5), to give the desired product (1.63g, 55%), δ (250MHz, d_4-MeOH), 1.46 (9H, s, $OC(Me)_3$), 1.95-2.18 (2H, m, CH_2), 3.34-3.51 (4H, m, 2 of CH_2), 4.22 (1H, m, C<u>H</u>OCH_2Ar), 4.59 (2H, s, O<u>CH_2</u>Ar), 7.43 (1H, dd, J=4.7 and 7.8Hz, Ar-H), 7.48 (1H, d, J=7.9Hz, Ar-H), 8.45-8.51 (2H, m, 2 of Ar-H).

b) (3R)-N-(H)-3-(pyridin-3-ylmethyloxy)pyrrolidine

Prepared from the preceding N-Boc pyrrolidine as described for Intermediate 2, part c, δ (250MHz, $CDCl_3$) 1.86-2.01 (2H, m, CH_2), 2.81-2.91 (2H, m, CH_2), 3.07-3.18 (2H, m, CH_2), 4.13 (1H, m, C<u>H</u>OCH_2Ar), 4.50 (2H, s, O<u>CH_2</u>Ar), 7.28 (1H, m, Ar-H), 7.68 (1H, m, Ar-H), 8.74-8.98 (2H, m, 2 of Ar-H).

c) (3R)-3-(Pyridin-3-ylmethyloxy)-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. Bisoxalate, 0.25 Hydrate.

Prepared from Intermediate 3 and the preceding N(H)-pyrrolidine using the procedure described for Example 2. The bisoxalate 0.25 hydrate salt was prepared which crystallised out containing a small amount of ether; m.p. 87-89°C. (Found: C, 54.53, H, 5.08, N, 14.58. $C_{22}H_{24}N_6O \cdot 2(C_2H_2O_4) \cdot 0.25\ H_2O \cdot 0.04(C_4H_{10}O)$ requires C, 54.55, H, 5.06, N, 14.59%). m/e 389 ($M+1^+$), δ (360MHz, d_6-DMSO) 2.08-2.30 (2H, m, CH_2), 3.10-3.15 (2H, m, CH_2), 3.38-3.50 (6H, m, CH_2), 4.37 (1H, br s, $CHOCH_2Ar$), 4.57 (2H, s, OCH_2Ar), 7.34-7.41 (3H, m, 3 of Ar-H), 7.53 (1H, d, J=8.7Hz, Ar-H), 7.78 (1H, br d, J=7.9Hz, Ar-H), 7.88 (1H, s, Ar-H), 8.50 (1H, m, Ar-H), 8.98 (1H, s, Ar-H), 9.02 (2H, s, Ar-H), 11.30 (1H, br s, NH).

EXAMPLE 4

(3R)-3-Benzyloxymethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl) ethyl]pyrrolidine. Hydrogen Oxalate Hemihydrate.

a) (3R)-N-*tert*-Butyloxycarbonyl-3-hydroxymethylpyrrolidine

Prepared from (3R)-N-[(R)-1-phenylethyl]-3-(hydroxymethyl) pyrrolidine (*J. Med. Chem.*, 1990, 33 (1), 71) as described for Example 1, part 2a, δ (250MHz, D_6-DMSO) 1.39 (9H, s, $OC(Me)_3$), 1.31-1.64 (2H, m, CH_2), 1.79-1.88 (1H, m, CH), 2.19-2.31 (1H, m, CH of CH_2), 2.95 (1H, dd, J=10.7 and 7.0Hz, CH of CH_2), 3.11-3.35 (4H, m, 2 of CH_2), 4.67 (1H, t, J=5.3Hz, OH).

b) (3R)-4-(3-Benzyloxymethyl)pyrrolidin-1-ylbutanal dimethyl acetal

The *title compound* was prepared from (3R)-N-*tert*-butyloxycarbonyl-3-hydroxymethylpyrrolidine as described for Example 1, parts 2b-d, δ (250MHz, D_6-DMSO) 1.24-1.56 (6H, m, 3 of CH_2), 1.75-1.89 (1H, m, CH), 2.21-2.55 (6H, m, 3 of CH_2), 3.20 (6H, s, CH $(OMe)_2$), 3.30

(2H, d, J=7.1Hz, $\underline{CH_2}OBn$), 4.34 (1H, t, J=5.3Hz, $C\underline{H}(OMe)_2$), 4.45 (2H, s, $O\underline{CH_2}Ar$), 7.24-7.39 (5H, m, Ar-H).

c) (3R)-3-Benzyloxymethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine, Hydrogen Oxalate, Hemihydrate.

A solution of Intermediate 1 (2.17g, 12.36mmol) and (3R)-4-(3-benzyloxymethyl)pyrrolidin-1-ylbutanal dimethyl acetal (3.80g, 12.36mmol) in 4% H_2SO_4 (30ml) was heated at reflux for 60h. The solution was cooled to room temperature and basified by addition of 4N NaOH solution and extracted with *n*-butanol (1 x 75ml). The solvent was removed under vacuum and the crude product chromatographed on silica eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1) to give the title-indole (0.45g 10%). The hydrogen oxalate hemihydrate salt was prepared: mp 145°C. (Found: C, 62.16; H, 5.97; N, 13.76. $C_{24}H_{27}N_5O \cdot C_2H_2O_4 \cdot 0.6\ H_2O$ requires C, 62.16; H, 6.06; N, 13.94%), δ (360MHz, D_6-DMSO) 1.64-1.78 (1H, m, CH of CH_2), 2.04-2.16 (1H, m, CH of CH_2), 2.60-2.72 (1H, m, CH), 3.04-3.50 (10H, m, 5 of CH_2), 4.49 (2H, s, $O\underline{CH_2}Ar$), 7.27-7.40 (7H, m, Ar-H), 7.52 (1H, d, J=8.6Hz, Ar-H), 7.90 (1H, d, J=2.0Hz, Ar-H), 9.04 (2H, s, Ar-H), 11.30 (1H, s, NH).

EXAMPLE 5

(3S)-3-(N-Benzyl-N-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine Sesquioxalate, 0.3 Hydrate.

a) (3R)-N-*tert*-Butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine

A solution of methane sulphonyl chloride (3.37g, 29.39mmol) in CH_2Cl_2 (30ml) was added dropwise to a solution of (3R)-N-*tert*-butyloxycarbonyl-3-hydroxymethylpyrrolidine (5.4g, 26.7mmol) and anhydrous triethylamine (2.97g, 29.39mmol), in CH_2Cl_2 (100ml), at -15°C. The mixture was warmed to room temperature and stirred for 16h before

adding saturated K_2CO_3 solution (50ml) and diluting with CH_2Cl_2 (100ml). The aqueous was separated and extracted further with CH_2Cl_2 (2 x 100ml). The combined extracts were dried (Na_2SO_4) and evaporated to give the title-mesylate (7.5g, 100%), δ (250MHz, $CDCl_3$) 1.46 (9H, s, $OC(Me)_3$), 1.62-1.84 (1H, m, CH of CH_2), 2.00-2.14 (1H, m, CH of CH_2), 2.58-2.72 (1H, m, CH), 3.04 (3H, s, Me), 3.08-3.62 (4H, m, 2 of CH_2), 4.11-4.33 (2H, m, CH_2OMs).

b) (3S)-N-*tert*-Butyloxycarbonyl-3-(N-benzyl-N-methyl) aminomethylpyrrolidine

A solution of the preceding mesylate (7.46g, 26.72mmol) in N-benzylmethylamine (22.7g, 187.0mmol) was heated at 100°C for 4h. The solvent was removed under vacuum, ethyl acetate (150ml) was added to the residue and the solution washed with water (100ml). The organic phase was dried (Na_2SO_4) and evaporated and the crude product chromatographed on silica gel eluting with CH_2Cl_2/MeOH (98:2) to give the title-N-methylbenzylamine (6.9g, 85%), δ (250MHz, $CDCl_3$) 1.46 (9H, s, $OC(Me)_3$), 1.50-1.72 (2H, m, CH_2), 1.90-2.02 (1H, m, CH), 2.21 (3H, s, NMe), 2.30-2.50 (2H, m, CH_2), 2.92-3.05 (1H, m, CH of CH_2), 3.18-3.62 (2H, m, 2 of CH_2 and CH of CH_2), 7.20-7.38 (5H, m, Ar-H).

c) (3S)-N(H)-3-(N-Benzyl-N-methyl)-aminomethylpyrrolidine

A solution of the preceding N-Boc pyrrolidine (6.9g, 22.7mmol) in trifluoroacetic acid (30ml) and CH_2Cl_2 (100ml) was stirred at room temperature for 16h. The solvents were removed under vacuum and the resulting residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (60:8:1) to give the title-product (4.6g, 99%), δ (250MHz, D_6-DMSO) 1.41-1.55 (1H, m, CH of CH_2), 1.89-2.02 (1H, m, CH of CH_2), 2.11 (3H, s, Me), 2.31 (2H, d, J=7.5Hz, CH_2NMe), 2.38-2.52 (1H, m, CH), 2.73 (1H, dd, J=11.3 and 6.9Hz, CH of CH_2), 2.95-3.23 (5H,

m, 2 of CH_2 and CH of CH_2), 3.46 (2H, ABq, J=13.4Hz, NCH_2Ar), 7.19-7.36 (5H, m, Ar-H).

d) (3S)-4-(3-(N-Benzyl-N-methyl)aminomethyl)-pyrrolidin-1-ylbutanal dimethyl acetal

A mixture of the preceding N(H)-pyrrolidine (3.0g, 14.68mmol), 4-chlorobutanal dimethyl acetal (2.24g, 14.68mmol), NaI (2.42g, 16.15mmol) and Na_2CO_3 (1.71g, 16.15mmol), in dimethoxyethane (50ml), was heated at reflux for 16h, in the absence of light. The solvent was removed under vacuum and ethyl acetate (100ml), water (70ml) and saturated K_2CO_3 solution (10ml) were added to the residue. The aqueous was separated and further extracted with EtOAc (2 x 100ml). The combined extracts were dried and evaporated and the residue chromatographed on silica gel eluting with CH_2Cl_2/iPA/NH_3 (80:8:1) to give the title-acetal (2.06g, 44%), δ (250MHz, D_6-DMSO) 1.23-1.55 (5H, m, 2 of CH_2 and CH), 1.75-1.89 (1H, m, CH of CH_2), 2.09 (3H, s, Me), 2.14-2.40 (9H, m, 4 of CH_2 and CH), 3.20 (6H, s, $(OMe)_2$), 3.42 (2H, ABq, J=13.3Hz NCH_2Ar), 4.33 (1H, t, J=5.4Hz, $CH(OMe)_2$) 7.19-7.35 (5H, m, Ar-H).

e) (3S)-3-(N-Benzyl-N-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine Sesquioxalate, 0.3 Hydrate.

Prepared from Intermediate 1 and the preceding acetal using the procedure described for Example 1. The sesquioxalate 0.3 hydrate salt was prepared; mp 116-117°C, (Found: C, 60.57; H, 6.47; N, 14.93. $C_{25}H_{30}N_6 \cdot 1.5(C_2H_2O_4) \cdot 0.3\ H_2O$ requires C, 60.59; H, 6.10; N, 15.14%); m/e 415 ($M+1^+$). δ (250MHz, $CDCl_3$ on free base) 1.44-1.60 (1H, m, CH of CH_2), 1.94-2.12 (1H, m, CH of CH_2), 2.20 (3H, s, Me), 2.31-3.01 (11H, m, 5 of CH_2 and CH), 3.48 (2H, ABq, J=13.2Hz, NCH_2Ar), 7.15 (1H, dd, J=8.6 and 2.1Hz, Ar-H), 7.19 (1H, d, J=2.3Hz, Ar-H), 7.19-7.26 (5H, m, Ar-H),

7.47 (1H, d, J=8.6Hz, Ar-H), 7.57 (1H, d, J=2.1Hz, Ar-H), 8.41 (1H, br s, NH), 8.47 (2H, s, Ar-H).

EXAMPLE 6

(2S)-2-(N-Benzyl-N-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. Sesquisuccinate. Sesquihydrate.

The *title compound* was prepared from (2S)-N-*tert*-butyloxycarbonyl-2-hydroxymethylpyrrolidine (L-prolinol from Aldrich) using the procedures described for the preparation of Example 5. The sesquisuccinate sesquihydrate salt was prepared, mp 70-72°C, (Found: C, 61.45, H, 6.65, N, 13.95. $C_{25}H_{30}N_6 \cdot 1.5(C_4H_6O_4) \cdot 1.5\ H_2O$ requires C, 61.52, H, 6.75, N, 13.89%), δ (360MHz, D_2O) 1.70-1.77 (1H, m, CH of CH_2), 1.85-1.93 (1H, m, CH of CH_2), 2.06-2.18 (1H, m, CH of CH_2), 2.22 (3H, s, Me), 2.22-2.33 (1H, m, CH of CH_2), 2.68-2.79 (2H, m, CH_2), 3.12-3.76 (9H, m, 4 of CH_2 and CH), 7.01-7.03 (2H, m, Ar-H), 7.15-7.21 (3H, m, Ar-H), 7.32 (1H, dd, J=8.6 and 2.1Hz, Ar-H), 7.47 (1H, s, Ar-H), 7.64 (1H, d, J=2.1Hz, Ar-H), 7.67 (1H, d, J=8.6Hz, Ar-H), 8.70 (2H, s, Ar-H).

EXAMPLE 7

(3S)-3-(N-Benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.6 Hydrogen Oxalate. 0.1 Hydrate.

a) (3S)-N(H)-3-(N-Benzyl)aminomethylpyrrolidine

Prepared from (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine and benzylamine as described for Example 5, parts b and c, δ (250MHz, $CDCl_3$) 1.38 (1H, m, CH), 1.90 (1H, m, CH), 2.24 (1H, qu, J=7.4Hz, CH), 2.54-2.62 (3H, m, CH_2 and CH of CH_2), 2.83-2.99 (2H, m, CH_2), 3.08 (1H, dd, J=7.6 and 11.0Hz, CH of CH_2), 3.80 (2H, s, CH_2Ar), 7.21-7.36 (5H, m, Ar-H).

b) (3S)-3-(N-Benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.6 Hydrogen Oxalate. 0.1 Hydrate.

Prepared from Intermediate 3 and the preceding N(H)-pyrrolidine using the procedure described for Example 2. The 2.6 hydrogen oxalate, 0.1 hydrate salt was prepared, mp 228-230°C. (Found, C, 55.16, H, 5.30, N, 13.00. $C_{24}H_{28}N_6 \cdot 2.6(C_2H_2O_4) \cdot 0.1\ H_2O$ requires C, 55.20, H, 5.29, N, 13.21%); m/e 401 ($M+1^+$), δ (360MHz, d_6-DMSO) 1.96 (1H, m, CH_2), 2.10 (1H, m, CH_2), 2.76 (1H, m, CH of CH_2), 3.00-3.24 (5H, m, CH_2), 3.30-3.60 (5H, m, CH_2), 4.14 (2H, s, CH_2Ar), 7.35-7.54 (8H, m, Ar-H), 7.91 (1H, s, Ar-H), 9.04 (2H, s, Ar-H), 11.30 (1H, br s, NH).

EXAMPLE 8

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[4-(acetylamino) benzylamino]piperidine. 2.85 Hydrogen Oxalate.

1. 5-Bromopentanal dimethyl acetal

To a solution of 5-bromovaleryl chloride (50g, 0.251mol) in anhydrous THF (500ml), at -78°C, was added lithium tri-*tert*-butoxyaluminohydride (1.0M solution in tetrahydrofuran, 300ml; 0.30mol), keeping the temperture below 70°C. The solution was stirred at -78°C for 5h and then quenched by dropwise addition of 2M hydrochloric acid (350ml). The mixture was warmed to room temperature and stirred for 16h. Diethyl ether (500ml) was added, the aqueous phase separated and extracted further with ether (x2). The combined extracts were washed with saturated Na_2CO_3 solution (x1), water (x1) and brine (x2), dried (Na_2SO_4) and evaporated to give 5-bromovaleraldehyde (37.5g, 91%). A solution of 5-bromovaleraldehyde (37.5g, 0.227mol) in methanol (250ml) and concentrated sulphuric acid (0.5ml) was stirred at room temperature for 3h. The solvent was removed under vacuum and to the residue was

added K_2CO_3 solution (50ml) and diethyl ether (500ml). The aqueous layer was separated and re-extracted with ether (x2). The combined extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica eluting with diethyl ether/hexane (1:9) to give the title-acetal (27.5g, 57%). δ (250MHz, $CDCl_3$) 1.43-1.67 (4H, m, 2 of CH_2), 1.83-1.94 (2H, m, CH_2), 3.38 (6H, s, $CH(OMe)_2$), 3.42 (2H, t, J=7Hz, CH_2Br), 4.37 (1H, t, J=7Hz, $\underline{C}H(OMe)_2$).

2. 5-(4-Hydroxypiperidin-1-yl)pentanal dimethyl acetal

A mixture of 5-bromopentanal dimethyl acetal (3.34g, 15.82mmol), anhydrous potassium carbonate (2.218g, 15.82mmol) and 4-hydroxypiperidine (2.0g, 19.77mmol) in anhydrous dimethylformamide (50ml) was stirred at 80-90°C for 3 hours under nitrogen. After cooling, the mixture was diluted with water (150ml), basified with saturated aqueous potassium carbonate and the product was extracted with ethyl acetate (3 x 250ml). The combined organic solutions were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/methanol/ammonia, 90:10:1) gave 2.71g (74%) of the *title compound* as a colourless oil, δ (250MHz, d_6-DMSO) 1.06-1.56 (8H, m), 1.62-1.75 (2H, m), 1.86-2.00 (2H, m), 3.20 (6H, s), 3.34-3.47 (1H, m), 4.31 (1H, t, J=5.7Hz), 4.53 (1H, d, J=4.2Hz), m/e (ES) 232 ($M+1^+$).

3. 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-hydroxypiperidine, 1.35 Hydrogen Oxalate.

A solution of the preceding dimethyl acetal (2.70g, 11.67mmol) and 4-(1,2,4-triazol-4-yl)phenylhydrazine (2.15g, 12.25mmol) in 4% sulphuric acid (100ml) was refluxed for 9h. After cooling to room temperature, the reaction mixture was basified with saturated aqueous potassium carbonate and products were extracted with ethyl acetate (3 x 250ml) and with a mixture of ethyl acetate and *n*-butanol (1:1, 2 x 250ml). The

combined organic solutions were washed with brine (1 x 50ml), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/methanol/ammonia, 85:15:1.5) gave 1.96g.(51.6%) of the *title compound* free base as a pale yellow foam. The oxalate salt was prepared and recrystallised from ethanol-diethyl ether, mp 102-105°C, (Found: C, 55.76, H, 5.99, N, 15.43. $C_{18}H_{23}N_5O \cdot 1.35(C_2H_2O_4)$ requires: C, 55.63, H, 5.80: N, 15.67%), δ (360MHz, D_2O) 7.31 (1H, dd, J=8.6 and 2.6Hz), 7.36 (1H, d, J=2.6Hz), 7.61 (1H, d, J=8.6Hz), 7.75 (1H, s), 8.87 (2H, s) among other signals, m/e (ES) 326 ($M+1^+$).

4. 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine

To a stirred solution of the preceding alcohol free base (105mg, 0.322mmol) in a mixture of anhydrous dimethyl sulfoxide (3ml) and anhydrous triethylamine (314µl, 2.25mmol) was added portionwise, under nitrogen, solid sulphur trioxide pyridine complex (185mg, 1.16mmol) over 7 minutes. After 55 minutes of stirring at room temperature, the mixture was diluted with water (20ml), basified with saturated aqueous potassium carbonate and extracted with ethyl acetate (3 x 70ml). The organic phases were combined, washed with brine (1 x 20ml), dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/methanol/ammonia, 90:10:1) afforded 72mg (69%) of the *title compound* as a waxy solid, δ (250MHz, $CDCl_3$) 1.96 (2H, qn, J=7.3Hz), 2.42-2.62 (6H, m), 2.72-2.90 (6H, m), 7.13-7.19 (2H, m), 7.50 (1H, d, J=8.5Hz), 7.57 (1H, d, J=2.0Hz), 8.42 (1H, br s), 8.48 (2H, s), m/e (ES) 324 ($M+1^+$).

5. 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[4-(acetylamino)benzylamino]piperidine. 2.85 Hydrogen Oxalate.

To a stirred solution of the preceding ketone (100mg, 0.309mmol) and 4-(acetylamino)benzylamine hydrochloride (111.5mg, 0.371mmol) in methanol (7ml) was added anhydrous triethylamine (51.7µl, 0.371mmol)

followed by glacial acetic acid (70.7µl, 1.236mmol). After 15 minutes, sodium cyanoborohydride (25mg) was added and stirring was continued at room temperature for 3.5 hours. Saturated aqueous potassium carbonate (4ml) was added and the methanol was removed under vacuum. The aqueous residue was diluted with brine (25ml) and products were extracted with ethyl acetate (1 x 50ml), chloroform (2 x 50ml) and chloroform-*n*-butanol (1:2; 1 x 150ml). The combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/methanol/ammonia, 85:15:1.5) gave 95mg (65%) of the *title compound* free base. The oxalate salt was prepared and crystallised from ethanol-diethyl ether, mp 205-210°C, (Found: C, 53.64, H, 5.26, N, 13.74. $C_{27}H_{33}N_7O \cdot 2.85(C_2H_2O_4)$ requires C, 53.94, H, 5.36, N, 13.46%), δ (360MHz, D_2O) 1.86-2.04 (2H, m), 2.10-2.24 (2H, m), 2.17 (3H, s), 2.45 (2H, br d, J=13Hz), 2.90 (2H, t, J=7.0Hz), 3.04 (2H, t, J=12Hz), 3.14-3.24 (2H, m), 3.55 (1H, br t), 3.71 (2H, br d, J=13Hz), 4.27 (2H, s), 7.32-7.40 (2H, m), 7.46 (2H, d, J=8.6Hz), 7.49 (2H, d, J=8.6Hz), 7.64 (1H, d, J=8.7Hz), 7.80 (1H, s), 9.02 (2H, s), m/e (ES) 472 ($M+1^+$).

EXAMPLE 9

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(benzylamino) piperidine. Dihydrogen Oxalate Dihydrate

The *title compound* was prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and benzylamine using a similar procedure to that described for Example 8 (step 5), mp 233-234°C, (Found: C, 55.49; H, 5.69; N, 13.26. $C_{25}H_{30}N_6 \cdot 2(C_2H_2O_4) \cdot 2\ H_2O$ requires C, 55.23; H, 6.07; N, 13.33%). δ (360MHz, d_6-DMSO) 1.85-2.00 (2H, m), 2.01-2.11 (2H, m), 2.19-2.22 (2H, m), 2.73-2.90 (4H, m), 2.91-3.00 (2H, m), 3.16-3.25 (1H, m), 3.4-3.5 (2H, m), 4.14 (2H, s), 7.30-7.33 (2H, m), 7.40-7.42 (3H, m),

7.48-7.51 (3H, m), 7.80-7.81 (1H, m), 9.02 (2H, s), 11.20 (1H, s), m/e (ES) 415 (M+1$^+$).

EXAMPLE 10

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[N-benzyl-N-methylamino]piperidine. 1.5 Hydrogen Oxalate.

To a stirred solution of the preceding amine (Example 9) (164mg, 0.396mmol), formaldehyde (38% wt in H_2O, 32μL, 0.436mmol) and glacial acetic acid (90mg, 1.584mmol) in methanol (10ml) was added sodium cyanoborohydride (27mg, 0.436mmol). Stirring was continued for 3h. Saturated aqueous potassium carbonate (4ml) was added and the methanol removed under vacuum. The aqueous residue was partitioned between ethyl acetate (30ml) and water (20ml). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, dichloromethane/methanol/ammonia, 90:10:1) gave 128mg (76%) of the *title compound* free base. The oxalate salt was prepared and crystallised from methanol-diethyl ether, mp 134-136°C; (Found: C, 59.39; H, 6.08; N, 14.10. $C_{26}H_{32}N_6 \cdot 1.5(C_2H_2O_4) \cdot 1.3\ H_2O$ requires, C, 59.33, H, 6.46, N, 14.31%); δ (360xMHz, d_6-DMSO) 1.74-1.88 (2H, m), 1.90-2.08 (4H, m), 2.16 (3H, s), 2.70-2.84 (5H, m), 2.92-3.02 (2H, m), 3.36-3.46 (2H, m), 3.65 (2H, s), 7.20-7.36 (7H, m), 7.50 (1H, d, 8.6Hz), 7.80 (1H, s), 9.02 (2H, s), 11.18 (1H, s). m/e (ES$^+$) 429 (M+1$^+$).

EXAMPLE 11

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(benzylamino) methyl]piperidine. 2.5 Hydrogen Oxalate.

1. 4-[(Benzylamino)methyl]piperidine

A solution of 4-(aminomethyl)piperidine (22.8g, 200mmol) and benzaldehyde (21.2g, 200mmol) in toluene (200ml) was refluxed for 5h, under nitrogen, using a Dean-Stark trap. After cooling, the toluene was removed under vacuum and the residual oil was dissolved in absolute ethanol (400ml) and cooled to 5°C. Sodium borohydride (6g, 158.7 mmol) was added portionwise to the above solution over 40 minutes, under nitrogen, and the mixture was stirred for a further 1 hour 15 minutes before excess borohydride was destroyed by dropwise addition of 5N hydrochloric acid (150ml) (CAUTION: hydrogen evolution). The ethanol was removed under vacuum and the aqueous residue was basified and extracted with ethyl acetate (5 x 500ml). The combined organic solutions were dried (Na_2SO_4) and concentrated. Column chromatography (alumina, activity II-III; dichloromethane/methanol/ammonia, 95:5:0.35) of the residue afforded 19.3g (47%) of the *title compound* as a pale yellow oil, δ (250MHz, d_6-DMSO) 1.13 (2H, dq, J=12 and 4.0Hz), 1.50-1.70 (1H, m), 1.78 (2H, br d, J=11Hz), 2.47 (2H, d, J=6.6Hz), 2.56 (2H, dt, J=12 and 2.3Hz), 3.05 (2H, br d, J=12Hz), 3.83 (2H, s), 7.30-7.50 (5H, m), m/e (ES) 205 ($M+1^+$).

2. <u>5-{4-[(Benzylamino)methyl]piperidin-1-yl}pentanal dimethyl acetal</u>

The *title compound* was prepared in 58% yield from 5-bromopentanal dimethyl acetal and 4-[(benzylamino)methyl]piperidine using a similar method to that described for Example 8 (step 2). δ (250MHz, d_6-DMSO) 1.26-2.14 (13H, m), 2.49 (2H, t, J=7.0Hz), 2.63 (2H, d, J=6.6Hz), 3.04-3.14 (2H, m), 3.49 (6H, s), 3.95 (2H, s), 4.61 (1H, t, J=5.7Hz), 7.44-7.62 (5H, m), m/e (ES) 335 ($M+1^+$).

3. <u>1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(benzylamino)methyl]piperidine, 2.5 Hydrogen Oxalate.</u>

A solution of the preceding acetal (2.70g, 8.07mmol) and 4′-(1,2,4-triazol-4-yl)phenylhydrazine (1.50g, 8.5mmol) in 4% H_2SO_4 (100ml) was

refluxed for 20 hours. After cooling, the mixture was basified with 4N sodium hydroxide and products were extracted with ethyl acetate (3 x 200ml). The combined organic solutions were washed with brine (1 x 50ml), dried (Na_2SO_4) and concentrated. Flash chromatogrpahy of the residue (silica gel, dichloromethane/methanol/ammonia, 90:10:0.9) gave 1.63g (47%) of the *title compound* free base as a thick pale yellow oil. The oxalate salt was prepared and recrystallised from ethanol-methanol, mp 215-220°C, (Found: C, 56.78; H, 5.56; N, 12.82. $C_{28}H_{32}N_6 \cdot 2.5(C_2H_2O_4)$ requires: C, 56.96; H, 5.71; N, 12.86%). δ (360MHz, d_6-DMSO) 1.36-1.56 (2H, m), 1.86-2.12 (5H, m), 2.70-2.94 (6H, m), 2.98-3.08 (2H, m), 3.36-3.50 (2H, m), 4.12 (2H, s), 7.30-7.54 (8H, m), 7.80(1H, s), 9.02 (2H, s), 11.95 (1H, s), m/e (ES) 429 ($M+1^+$).

EXAMPLE 12

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(N-benzyl-N-methylamino)methyl]piperidine. 2.65 Hydrogen Oxalate.

The *title compound* was prepared in 73% isolated yield from the product of Example 11 using a similiar procedure to that described for Example 10. The oxalate salt was prepared and recrystallised from ethanol, mp 131-134°C. (Found: C, 56.96; H, 5.84; N, 12.21. $C_{27}H_{34}N_6 \cdot 2.56(C_2H_2O_4)$ requires: C, 56.95; H, 5.82; N, 12.34%), δ (360MHz, DMSO-d_6) 2.29 (3H, s), 3.72 (2H, s), 7.40-7.24 (7H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, d, J=1.9Hz), 9.02 (2H, s), 11.19 (1H, s) among other signals; m/e (ES) 443 (M^++1).

Examples 13 - 20 were prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and the corresponding commercially available amines using a similar method to that described for Example 8 (step 5).

EXAMPLE 13

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(methyl) benzylamine]piperidine. 2.7 Hydrogen Oxalate. 0.4 Hydrate.

The oxalate salt was prepared from ethanol, mp 111-115°C. (Found: C, 55.62; H, 5.82; N, 12.04. $C_{28}H_{32}N_6 \cdot 2.7(C_2H_2O_4) \cdot 0.4\ H_2O$ requires: C, 55.55; H, 5.67; N, 12.38%.) δ (360MHz, DMSO-d_6) 1.51 (3H, d, J=6.5Hz), 1.74-2.22 (6H, m), 2.64-2.96 (7H, m), 3.34-3.48 (2H, m), 4.42 (1H, br q, J=6.5Hz), 7.28-7.68 (8H, m), 7.78 (1H, d, J=2.0Hz), 9.01 (2H, s), 11.17 (1H, s); m/e (ES) 429 $(M+1)^+$; $[\alpha]_D$ + 24 (c 0.52, MeOH).

EXAMPLE 14

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(S)-α-(methyl) benzylamino]piperidine. 2.7 Hydrogen Oxalate. 0.3 Hydrate.

The oxalate salt was prepared from ethanol, mp 121-125°C. (Found: C, 56.51; H, 5.86; N, 12.57. $C_{28}H_{32}N_6 \cdot 2.5(C_2H_2O_4) \cdot 0.3\ H_2O$ requires: C, 56.49; H, 5.75; N, 12.75%). $[\alpha]_D$ - 23.9 (c 0.51, MeOH).

EXAMPLE 15

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(S)-α-(hydroxymethyl)benzylamino]piperidine. 2.6 Hydrogen Oxalate.

The oxalate salt was prepared from methanol-diethyl ether, mp 175-180°C. (Found: C, 54.92; H, 5.49; N, 12.59. $C_{26}H_{32}N_6 \cdot 2.6(C_2H_2O_4)$ requires: C, 55.22; H, 5.53; N, 12.38%). δ (360MHz, DMSO-d_6) 1.62-1.84 (2H, m), 1.90-2.16 (4H, m), 2.60-2.96 (7H, m), 3.28-3.42 (2H, m), 3.63 (2H, br s), 4.19 (1H, m), 7.36-7.54 (8H, m), 7.78 (1H, d, J=2.0Hz), 9.01 (2H, s), 11.17 (1H, s); m/e (ES) 445 $(M^+ + 1)$.

EXAMPLE 16

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(hydroxymethyl) benzylamino]piperidine. 1.9 Hydrogen Oxalate. Monohydrate.

The oxalate salt was prepared from methanol-diethyl ether, mp 154-157°C. (Found: C, 56.69; H, 6.20; N, 12.91. $C_{28}H_{32}N_6O \cdot 1.9(C_2H_2O_4) \cdot 1.0\ H_2O \cdot 0.15(C_4H_{10}O)$ requires: C, 56.63; H, 6.14; N, 13.03%).

EXAMPLE 17

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{(S)-[1-hydroxymethyl-2-phenylethylamino]piperidine. 2.0 Hydrogen Oxalate. 1.4 Hydrate.

The oxalate salt was prepared from methanol-diethyl ether, mp 180-185°C. (Found: C, 56.14; H, 6.10; N, 12.83. $C_{27}H_{34}N_6O \cdot 2.0(C_2H_2O_4) \cdot 1.4\ H_2O$ requires: C, 56.08; H, 6.19; N, 12.66%). δ (360MHz, DMSO-d_6) 1.68-1.86 (2H, m), 1.94-2.18 (4H, m), 2.54-3.00 (8H, m), 3.24-3.40 (5H, m), 3.53 (1H, d, J=9.5Hz), 7.20-7.36 (7H, m), 7.49 (1H, d, J=8.6Hz), 7.80 (1H, d, J=2.0Hz), 9.02 (2H, s), 11.17 (1H, s); m/e (ES) 459 (M^++1).

EXAMPLE 18

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{(1R,2S)-[2-hydroxy-1-methyl-2-phenyl]ethylamino}piperidine. 2.3 Hydrogen Oxalate. Monohydrate.

The oxalate salt was prepared from methanol-diethyl ether, mp 148-152°C. (Found: C, 55.48; H, 6.16; N, 12.23. $C_{27}H_{34}N_6O \cdot 2.3(C_2H_2O_4) \cdot 1.0\ H_2O$. $0.15(C_4H_{10}O)$ requires: C, 55.66; H, 6.12; N, 12.10%). δ (360MHz, DMSO-d_6) 0.92 (3H, d, J=6.5Hz), 1.70-1.86 (2H, m), 1.90-2.04 (2H, m),

2.08-2.30 (2H, m), 2.52-2.86 (5H, m), 3.23-3.52 (5H, m), 5.07 (1H, s), 7.22-7.44 (7H, m), 7.50 (1H, d, J=8.6Hz), 7.80 (1H, d, J=2.0Hz), 9.02 (2H, s), 11.17 (1H, s); m/e (ES) 459 (M^++1).

EXAMPLE 19

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{(1S,2R)-[2-hydroxy-1-methyl-2-phenyl]ethylamino}piperidine. 2.1 Hydrogen Oxalate.

The oxalate salt was prepared from methanol-diethyl ether, mp 148-151°C. (Found: C, 56.36; H, 6.16; N, 12.58. $C_{27}H_{34}N_6O \cdot 2.1(C_2H_2O_4).0.1(C_4H_{10}O)$ requires: C, 56.39; H, 6.17; N, 12.49%). m/e (ES) 459 (M^++1).

EXAMPLE 20

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{(1R,2R)-[2-hydroxy-1-methyl-2-phenyl]ethylamino}piperidine. 2.4 Hydrogen Oxalate. 1.1 Hydrate.

The oxalate salt was prepared from methanol-diethyl ether, mp 125-128°C. (Found: C, 55.12; H, 6.47; N, 11.82. $C_{27}H_{34}N_6O.2.4(C_2H_2O_4)\cdot 1.1\ H_2O\cdot 0.2(C_4H_{10}O)$ requires: C, 55.20; H, 6.11; N, 11.85%). δ (360MHz, DMSO-d_6) 0.94 (3H, d, J=6.6Hz), 1.76-2.24 (6H, m), 2.70-2.84 (4H, m), 2.86-2.98 (2H, m), 3.30-3.47 (4H, m), 4.51 (1H, d, J=9.0Hz), 7.28-7.42 (7H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, d, J=2.0Hz), 9.03 (2H, s), 11.19 (1H, s); m/e (ES) 459 (M^++1).

EXAMPLE 21

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[2-(4-acetylaminophenyl)ethyl]amino}piperidine. 2.4 Hydrogen Oxalate. Monohydrate.

a) 4-(Acetylamino)phenethylamine

To a cooled (0°C) and stirred solution of 4-aminobenzyl cyanide (2.38g, 18.04mmol) in anhydrous dichloromethane (30ml) was added anhydrous triethylamine (7.54ml, 54.12mmol) followed by acetic anhydride (2.56ml, 27.06mmol) under nitrogen. The mixture was allowed to warm to room temperature and it was stirred for 18h before it was diluted with ethyl acetate (150ml) and washed with 10% aqueous sodium bicarbonate (100ml), 2M hydrochloric acid (50ml), brine (50ml), then dried ($MgSO_4$) and concentrated to give 4-(acetylamino)benzyl cyanide as an orange solid. The crude nitrile (2.8g) was dissolved in absolute ethanol (200ml) and chloroform (4ml) and it was hydrogenated at 50 psi over platinum (IV) oxide for 16h. The catalyst was filtered off, washed with ethanol and the filtrate was concentrated under vacuum. The residue was dissolved in 2M sodium hydroxide (30ml) and the product was extracted with dichloromethane (4 x 150ml), then dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/ methanol/ammonia, 85:15:1.5) gave 2.3g (80%) of the *title compound* as a yellow solid. δ (360MHz, $CDCl_3$) 2.16 (3H, s), 2.71 (2H, t, J=6.8Hz), 2.94 (2H, t, J=6.8Hz), 7.14 (2H, d, J=8.3Hz), 7.26 (1H, br s), 7.41 (2H, d, J=8.3Hz).

b) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[2-(4-acetylaminophenyl)ethyl]amino}piperidine. 2.4 Hydrogen Oxalate. Monohydrate.

The *title compound* was prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and 4-(acetylamino)phenylamine using a similar method to that described for Example 8 (step 5). Oxalate salt prepared from methanol-diethyl ether, mp 195-202°C. (Found: C, 54.87; H, 5.68; N, 13.83. $C_{28}H_{35}N_7O \cdot 2.4(C_2H_2O_4) \cdot 1.0\ H_2O$ requires: C, 54.74; H, 5.85; N, 13.62%). δ (360MHz, DMSO-d_6) 1.70-1.86 (2H, m),

2.94-2.22 (5H, m and s), 2.60-2.94 (8H, m), 3.06-3.28 (3H, m), 3.34-3.44 (1H, m), 7.18 (2H, d, J=8.4Hz), 7.28-7.36 (2H, m), 7.46-7.56 (3H, m), 7.80 (1H, d, J=2.0Hz), 9.02 (2H, s), 9.92 (1H, s), 11.17 (1H, s); m/e (ES) 486 (M^++1).

EXAMPLE 22

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R)-α-(methyl) benzylamino]methyl}piperidine. Hydrogen Oxalate. 2.6 Hydrate.

a) 5-[4-(Hydroxymethyl)piperidin-1-yl]pentanal dimethyl acetal

To a cooled (0°C) and stirred suspension of isonipecotic acid (25.83g, 200mmol), in anhydrous THF (100ml) was added lithium aluminium hydride (1M in THF; 200ml), under a nitrogen atmosphere. The reaction was allowed to attain room temperature and it was stirred for 18h, then refluxed for a further 4h. The reaction was quenched by sequential addition of water (7.5ml), 15% sodium hydroxide solution (7.5ml) and water (15ml). The reaction was filtered to remove a granular precipitate and the filtrate was concentrated under vacuum to give 11.24g of 4-(hydroxymethyl)piperidine as a colourless oil. The *title compound* was prepared from 5-chloropentanal dimethyl acetal (20.4g, 122mmol) and 4-(hydroxymethyl)piperidine (15.7g) using a similar method to that described for Example 8 (step 2). δ (360MHz, DMSO-d_6) 1.10 (2H, m), 1.28 (2H, m), 1.39 (2H, m), 1.48 (2H, m), 1.60 (2H, br d), 1.77 (2H, t), 2.20 (2H, t), 2.80 (2H, br d), 3.21 (8H, m), 4.31 (1H, t), 4.37 (1H, t).

b) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(hydroxymethyl) piperidine

The *title compound* was prepared from the preceding dimethyl acetal (18.64g, 76mmol) and 4'-(1,2,4-triazol-4-yl)phenyl hydrazine (15.98g) using a similar method to that described for Example 8 (step 3).

δ (250MHz, DMSO-d_6) 1.11 (2H, m), 1.30 (1H, m), 1.60 (2H, d), 1.80 (4H, m), 2.29 (2H, t), 2.70 (2H, t), 2.84 (2H, d), 3.22 (2H, t), 4.40 (1H, t), 7.26-7.31 (2H, m), 7.46 (1H, d), 7.78 (1H, d), 9.02 (2H, s), 11.08 (1H, s).

c) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R)-α-(methyl)benzylaminolmethyl}piperidine, Hydrogen Oxalate, 2.6 Hydrate.

To a solution of the preceding alcohol (0.5g, 1.48mmol) in a mixture of anhydrous dimethyl sulphoxide (20ml) and anhydrous triethylamine (755µl, 10.29mmol) was added portionwise, under nitrogen, solid sulphur trioxide pyridine complex, (844mg, 5.3mmol). After 2 hours of stirring, the reaction was cooled to 0°C, quenched by dropwise addition of saturated aqueous potassium carbonate (5ml) and it was partitioned between water-butanol (30ml-70ml). The organic phase was concentrated to 5ml under vacuum and diluted with methanol (10ml). Acetic acid (506µl) and (R)-α-methylbenzylamine (209µl, 1.62mmol) were added followed, after 10 minutes, by sodium cyanoborohydride (102mg). After 18h of stirring, the reaction was quenched with saturated aqueous potassium carbonate, volatiles removed *in vacuo* and the residue was partitioned between water-butanol. The organic phase was concentrated and purified by flash chromatography (silica gel, dichloromethane/methanol/ammonia, 92:8:1) to give 85mg of the *title compound* free base as a colourless solid. The oxalate salt was prepared and crystallised from methanol/diethyl/ether, mp 140°C. (Found: C, 59.86; H, 6.81; N, 14.37. $C_{27}H_{34}N_6 \cdot C_2H_2O_4 \cdot 2.6\ H_2O$ requires: C, 59.90; H, 6.93; N, 14.45%). δ (360MHz, DMSO-d_6) 1.20 (2H, m), 1.39 (3H, d), 1.58 (1H, m), 1.76 (2H, brt), 1.92 (2H, m), 2.27-2.30(3H, m), 2.69-2.72 (5H, m), 3.12-3.16 (2H, m), 3.97 (1H, d), 7.29-7.50 (8H,m), 7.78 (1H, d), 9.02 (2H, s), 11.16 (1H, s); m/e (ES) 443 (M^++1). HPLC analysis on a Chiralpak AD column, using hexane/ethanol/diethylamine (25:75:0.1) as the mobile phase (UV detection at 280nm; flow 1ml/min; 40°C) showed the compound to have a retention time of 6.4min.

EXAMPLE 23

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(S)-α-(methyl) benzylamino]methyl}piperidine. 1.5 Hydrogen Oxalate. Monohydrate.

The *title compound* was prepared using a similar procedure to that described for Example 22. The oxalate salt was prepared and recrystallised from methanol-diethyl ether, mp. 149-150°C. (Found: C, 60.11; H, 6.92; N, 14.51. $C_{27}H_{34}N_6 \cdot 1.5(C_2H_2O_4) \cdot H_2O$ requires: C, 60.49; H, 6.60; N, 14.11%). Other spectroscopic data identical to product from Example 22. HPLC analysis retention time = 8.3min (see Example 22 for conditions).

EXAMPLE 24

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(S)-1-(4-acetylaminophenyl)ethylamino]methyl}piperidine. 2.0 Hydrogen Oxalate. 2.0 Hydrate.

a) N-*tert*-Butyloxycarbonyl-(S)-1-(4-nitrophenyl)ethylamine

To a suspension of (S)-1-(4-nitrophenyl)ethylamine hydrochloride (2.12g, 10.4mmol) in anhydrous dichloromethane (50ml) was added triethylamine (1.45ml). A solution of di-*tert*-butyldicarbonate (2.28g) in anhydrous dichloromethane (50ml) was added and the reaction allowed to stand for 18h. The reaction was washed with water, dried ($MgSO_4$), concentrated and purified by chromatography on silica gel using 1:1 ethyl acetate:petroleum ether as eluant. The *title compound* was obtained as a yellow oil which crystallised slowly.

b) N-*tert*-Butyloxycarbonyl-(S)-1-(4-acetamidophenyl)ethylamine

A solution of the product from above (2.96g) in ethyl acetate (100ml) was hydrogenolysed over PtO_2 (0.11g) at 15psi for 50 minutes in the

presence of acetic anhydride (0.97ml). The catalyst was removed by filtration and washed with ethanol. The filtrate was concentrated to give the *title compound*. δ (250MHz, D_6-DMSO) 1.26 (3H, d, J=10Hz), 1.35 (9H, s), 2.02 (3H, s), 4.54 (1H, m), 7.19 (2H, d, J=12.9Hz), 7.30 (1H, d, J=11.6Hz), 7.47 (2H, d, J=12.2Hz).

c) (S)-1-(4-Acetamidophenyl)ethylamine

The product from above (1.89g, 6.8mmol) was dissolved in 90% formic acid (5ml) and was stirred at room temperature, until all the starting material had reacted. The reaction was concentrated, basified with saturated potassium carbonate solution and extracted into butanol. The solvent was removed to give the *title compound* as a brown foam, which could be crystallised from methanol-ethyl acetate. δ (360MHz, D_6-DMSO) 1.28 (3H, d, J=6.6Hz), 2.02 (3H, s), 4.03 (1H, m), 7.29 (2H, d, J=8.6Hz), 7.50 (2H, d, J=8.6Hz), 8.46 (2H, br s), 10.02 (1H, s).

d) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(S)-1-(4-acetylaminophenyl)ethylamino]methyl}piperidine. 2.0 Hydrogen Oxalate. 2.0 Hydrate.

The *title compound* was prepared from the amine described above using a similar procedure to that described in Example 22 (step 4). The oxalate salt was prepared and recrystallised from methanol-diethyl ether to give a hygroscopic solid; (Found: C, 55.41; H, 6.12; N, 13.38. $C_{29}H_{37}N_7O \cdot 2(C_2H_2O_4) \cdot 2\ H_2O$ requires: C, 55.37; H, 6.33; N, 13.69%). δ (360MHz, D_6-DMSO) 1.2-1.4 (2H, m), 1.44 (3H, d, J=6.7Hz), 1.8-2.0 (3H, m), 1.8-2.1 (5H, m), 2.37 (2H, m), 2.37-2.6 (2H, m), 2.7-2.9 (4H, m), 3.0-3.1 (2H, m), 3.3-3.5 (1H, m), 4.0-4.1 (1H, br s), 7.31-7.36 (4H, m,), 7.49-7.51 (1H, d, J=8.6Hz), 7.56-7.59 (2H, m), 7.80 (1H, s), 9.07 (2H, s), 10.01 (1H, s), 11.19 (1H, s); m/e (ES^+) 450 $(M+1)^+$.

EXAMPLE 25

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R)-1-(4-acetylaminophenyl)ethyl]amino}piperidine. 3.0 Hydrogen Oxalate. 1.2 Hydrate.

The *title compound* was prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and (R)-1-(4-acetamidophenyl) ethylamine using a similar method to that decribed for Example 8 (step 5). The oxalate salt was prepared from methanol-diethyl ether, mp 135-140°C. (Found: C, 52.51; H, 5.79; N, 12.59. $C_{28}H_{35}N_7O \cdot 3.0(C_2H_2O_4) \cdot 1.2\ H_2O \cdot 0.2(C_4H_{10}O)$ requires: C, 52.76; H, 5.78; N, 12.38%). δ (360MHz, D_6-DMSO) 1.50 (3H, d, J=6.5Hz), 1.72-1.90 (2H, m), 1.92-2.20 (7H, m and s), 2.62-2.96 (7H, m), 3.32-3.44 (2H, m), 4.34-4.42 (1H, m), 7.29 (1H, s), 7.31 (1H, d, J=8.6Hz), 7.45 (2H, d, J=8.6Hz), 7.48 (1H, d, J=8.6Hz), 7.61 (2H, d, J=8.6Hz), 7.78 (1H, d, J=2.0Hz), 9.01 (2H, s), 10.6 (1H, s), 11.16 (1H, s); m/e (ES) 486 $(M+1)^+$.

Examples 26-28 were prepared from the products of Examples 15, 16 and 21 using a similar method to that described for Example 10.

EXAMPLE 26

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N-[(R)-α-(hydroxymethyl)benzyl]-N-methylamino}piperidine. 2.0 Hydrogen Oxalate. 1.4 Hydrate.

The oxalate salt was prepared from methanol-diethyl ether, mp 105-110°C. (Found: C, 56.13; H, 6.24; N, 12.34. $C_{27}H_{34}N_6O \cdot 2.0(C_2H_2O_4) \cdot 1.4\ H_2O \cdot 0.1(C_4H_{10}O)$ requires: C, 56.18, H, 6.28; N, 12.34%). δ (360MHz, DMSO-d_6) 1.78-2.08 (6H, m) 2.28 (3H, s), 2.70-3.06 (7H, m), 3.38-3.48 (2H, m), 3.72 (1H, dd, J=11.3 and 5.1Hz), 3.85 (1H, dd, J=11.3

and 6.1Hz), 4.01 (1H, m), 7.24-7.42 (7H, m), 7.49 (1H, d, J=8.5Hz), 7.79 (1H, d, J=2.0Hz), 9.01 (2H, s), 11.18 (1H, s); m/e (ES) 459 (M^+ +1).

EXAMPLE 27

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N-[(S)-α-(hydroxymethyl)benzyl]-N-methylamino}piperidine.
2.9 Hydrogen Oxalate. Monohydrate.

The oxalate salt was prepared from methanol-diethyl ether, mp 95-100°C. (Found: C, 53.37; H, 5.78, N, 11.49. $C_{27}H_{34}N_6O \cdot 2.9(C_2H_2O_4) \cdot 0.1(C_4H_{10}O)$ requires: C, 53.52; H, 5.79; N, 11.28%). m/e (ES) 459 (M^+ +1).

EXAMPLE 28

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N-[2-(4-acetylaminophenyl)ethyl]-N-methylamino}piperidine.
3.0 Hydrogen Oxalate. 1.1 Hydrate.

The oxalate salt was prepared from methanol-ether, mp 128-135°C. (Found: C, 53.36; H, 6.01; N, 12.19. $C_{28}H_{35}N_7O \cdot 3.0(C_2H_2O_4) \cdot 1.1\ H_2O \cdot 0.2(C_4H_{10}O)$ requires: C, 53.45; H, 5.91; N, 12.19%). δ (360MHz, DMSO-d_6) 1.80-2.12 (9H, m), 2.62 (3H, s), 2.70-2.90 (6H, m), 2.91-3.01 (2H, m), 3.03-3.12 (2H, m), 3.18-3.30 (1H, m), 3.39-3.52 (2H, m), 7.16-7.22 (2H, m), 7.29-7.36 (2H, m), 7.46-7.54 (3H, m), 7.80 (1H, d, J=2.0Hz), 9.02 (2H, s) 9.89 (1H, s), 11.18 (1H, s); m/e (ES) 500 (M^+ +1).

EXAMPLE 29

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[N-(4-acetylaminobenzyl)-N-methylamino]methyl}piperidine.

3.7 Hydrogen Oxalate.

a) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(N-methylamino)methyl]piperidine

A solution of the product from Example 12 (free base; 730mg) in absolute ethanol (60ml) was hydrogenated over 20% Pearlman's catalyst (500mg) for 24h at 45psi. The catalyst was filtered off, washed with ethanol (3 x 30ml) and the filtrate was concentrated under vacuum to give 573mg (99%) of the *title compound* as a yellow foam; m/e (ES) 353 (M^+ +1).

b) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[N-(4-acetylaminobenzyl)-N-methylamino]methyl}piperidine.
3.7 Hydrogen Oxalate.

The *title compound* was prepared from the product of the preceding step and 4-acetamidobenzaldehyde using a similar method to that described for Example 10. The oxalate salt was prepared, mp 155-165°C. (Found: C, 52.57; H, 5.47; N, 11.78. $C_{28}H_{37}N_7O \cdot 3.7(C_2H_2O_4)$ requires: C, 52.50; H, 5.37; N, 11.77%). δ (360MHz, DMSO-d_6) 1.23-1.42 (2H, m), 1.85-2.10 (8H, m and s), 2.39 (3H, s), 2.50-2.62 (2H, m), 2.72-2.96 (4H, m), 3.00-3.10 (2H, m), 3.36-3.54 (2H, m), 3.82 (2H, s), 7.28-7.36 (4H, m), 7.50 (1H, d, J=8.6Hz), 7.58 (2H, d, J=8.4Hz), 7.80 (1H, d, J=2.0Hz), 9.02 (2H, s), 10.01 (1H, s), 11.19 (1H, s); m/e (ES) 500 (M^+ +1).

EXAMPLE 30

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[N-[(thiophen-2-yl)methyl]-N-methylamino]piperidine. 2.0 Hydrogen Oxalate. Monohydrate.

a) 1-Benzyl-4-(N-*tert*-butyloxycarbonyl-N-methylamino)piperidine

To a cooled (0°C) and stirred solution of 1-benzyl-4-aminopiperidine (100g, 0.53mol) in anhydrous dichloromethane (500ml) was added a solution of di-*tert*-butyldicarbonate (126g) in anhydrous dichloromethane (500ml). The reaction was allowed to attain room temperature and stirred overnight. Concentration and trituration with diethyl ether gave 1-benzyl-4-(N-*tert*-butyloxycarbonylamino)piperidine.

To a cooled (-5°C) and stirred solution of lithium aluminium hydride (1M in THF; 258ml) in anhydrous tetrahydrofuran (250ml) was added a solution of the above amine (50g, 172mmol) in anhydrous tetrahydrofuran (750ml) over 20 minutes under nitrogen. The reaction mixture was then refluxed for 2.5 hours, cooled to room temperature and quenched by addition of water (10ml), 15% aqueous sodium hydroxide (15ml) and water (30ml). The resulting mixture was filtered to remove a granular precipitate and the filtrate was cooled to 0°C before di-*tert*-butyldicarbonate (41.3g) was added. After 2 hours at room temperature, the solvent was removed under vacuum and the residue was partitioned between 2N aqueous sodium hydroxide and dichloromethane. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/methanol/ammonia, 89:10:1) gave the *title compound*. δ (250MHz, DMSO-d_6) 1.38-1.49 (12H, m and s), 1.66 (2H, m), 1.94 (2H, m), 2.65 (3H, s), 2.90 (2H, br d), 3.44 (2H, s), 7.19-7.35 (5H, m).

b) 5-[4-(N-*tert*-Butyloxycarbonyl-N-methylamino)piperidin-1-yl]pentanal dimethyl acetal

A solution of the preceding benzylic amine (5g, 16.4mmol) in methanol (100ml) was hydrogenolysed over 10% palladium hydroxide (1g) at 50psi for 18 hours. The catalyst was filtered off and the filtrate was concentrated to give 4-(N-*tert*-butyloxycarbonyl-N-methylamino) piperidine as a colourless oil.

The *title compound* was prepared from the above amine and 5-bromopentanal dimethyl acetal using a similar method to that described for Example 8 (Step 2). δ (360MHz, $CDCl_3$) 1.34 (1H, m), 1.46-1.73 (19H, m and s), 1.98 (2H, m), 1.33 (2H, m), 2.73 (3H, s), 2.99 (2H, m), 3.31 (6H, s), 4.36 (1H, t).

c) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(N-methylamino)piperidine

The preceding acetal was reacted in a similar manner to that described in Example 11 (Step 3) to give the *title compound* as a brown foam. δ (360MHz, DMSO-d_6) 1.16-1.24 (3H, m), 1.73-1.90 (6H, m), 2.25 (6H, m), 2.70 (2H, t), 2.78 (2H, m), 7.28 (2H, m), 7.46 (1H, d), 7.77 (1H, d), 9.01 (2H, s), 11.08 (1H, s).

d) 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N-[(thiophen-2-yl)methyl]-N-methylamino}piperidine, 2.0 Hydrogen oxalate, Monohydrate.

To a solution of the preceding amine (390mg, 1.15mmol), acetic acid (0.2ml) and thiophen-2-carboxaldehyde (0.12ml) in anhydrous ethanol (10ml) was added sodium cyanoborohydride (80mg). The reaction was allowed to stir under a nitrogen atmosphere for 18h. The reaction was quenched by addition of saturated aqueous K_2CO_3 solution, concentrated to remove the ethanol, and extracted with butanol. Concentration and purification of the residue by chromatography on silica gel using

methanol/dichloromethane/ammonia (10:90:1) as eluant gave the *title compound* free base (306mg). The oxalate salt was prepared and crystallised from methanol-diethyl ether, m.p. 132-135°C, (Found: C, 53.31; H, 5.64; N, 12.59. $C_{24}H_{30}N_6S \cdot 2(C_2H_2O_4) \cdot H_2O \cdot 0.2(C_4H_{10}O)$ requires: C, 53.42; H, 5.91; N, 12.98%). δ (360MHz, D_2O) 2.00-2.20 (4H, m), 2.18-2.50 (2H, m), 2.82 (3H, s), 2.84-2.90 (2H, m), 3.0-3.10 (2H, m), 3.10-3.20 (2H, m), 3.60-3.80 (3H, m), 4.66 (2H, s), 7.16-7.18 (1H, m), 7.30-7.36 (3H, m), 7.61-7.65 (2H, m), 7.75 (1H, s), 8.88 (2H, s); m/e (ES$^+$) 435 (M+ 1$^+$).

EXAMPLE 31

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R)-α-(hydroxymethyl)benzylamino]methyl}piperidine. 1.5 Hydrogen Oxalate. Dihydrate.

The *title compound* was prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-(hydroxymethyl)piperidine and (R)-2-phenylglycinol using a similar method to that described for Example 22 (Step 4). The oxalate salt was prepared and recrystallised from methanol-diethyl ether, mp 143-145°C. (Found: C, 56.83; H, 6.92; N, 13.49. $C_{27}H_{34}N_6O \cdot 1.5\ (C_2H_2O_4) \cdot 2.0\ H_2O$ requires: C, 57.22; H, 6.56; N, 13.35%). δ (360MHz, DMSO-d_6) 1.26 (2H, m), 1.61 (1H, m), 1.73 (1H, m), 1.88 (1H, m), 1.97 (2H, m), 2.37 (1H, m), 2.49 (1H, m), 2.60 (2H, m), 2.74 (2H, t), 2.87 (2H, m), 3.25 (2H, m), 3.41 (1H, m), 3.50 (1H, m), 3.75 (1H, m), 7.26-7.36 (7H, m), 7.49 (1H, d), 7.79 (1H, d), 9.01 (2H, s), 11.17 (1H, s); m/e (ES) 459 (M$^+$ +1).

EXAMPLE 32

(3S)-3-(4-(Acetylamino)benzylamino)methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.6 Hydrogen Oxalate. 0.1 Hydrate.

a) (3S)-3-Aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine

A mixture of (3S)-3-(N-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine (Example 7; 0.277g, 0.639mmol), ammonium formate (0.218g, 3.46mmol) and 10% Pd-C (0.28g), in anhydrous methanol (20ml) was stirred at 62°C for 0.75h. The mixture was cooled to 25°C and the catalyst removed filtration through celite. The solvent was removed under vacuum and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (20:8:1) to give the *title compound* (0.145g, 68%), δ (250MHz, $CDCl_3$) 1.48-1.59 (1H, m, CH of CH_2), 2.03-2.14 (1H, m, CH of CH_2), 2.29-2.41 (2H, m, 2 of CH), 2.63-3.02 (9H, m, 4 of CH_2 and CH), 7.14 (1H, dd, J=2.1 and 8.6Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.49 (1H, d, J=8.6Hz, Ar-H), 7.60 (1H, d, J=2.1Hz, Ar-H), 8.54 (2H, s, Ar-H).

b) (3S)-3-(4-Acetylamino)benzylamino)methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.6 Hydrogen Oxalate, 0.1 Hydrate.

To a solution of the preceding aminomethyl pyrrolidine (0.14g, 0.452mmol) in ethanol (10ml) was added *p*-acetamidobenzaldehyde (0.074g, 0.452mmol) and the mixture stirred at 25°C for 16h. Sodium borohydride (17mg, 0.456mmol) was added and the solution stirred for 1h. The solvent was removed under vacuum and the residue was taken up into H_2O and acidified with 2N HCl. The mixture was then basified with saturated K_2CO_3 solution and extracted with ethyl acetate (x4). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (70:8:1) to give the title product (73mg, 35%). The 2.6 hydrogen oxalate 0.1 hydrate salt was prepared, mp 197-199°C. (Found: C, 54.22, H, 5.50, N, 14.12. $C_{26}H_{31}N_7O \cdot 2.6(C_2H_2O_4) \cdot 0.1\ H_2O$ requires C, 54.04; H, 5.29; N, 14.14%), m/e 458 $(M+1)^+$. δ (250MHz, D_6-DMSO)

1.66-1.86 (1H, m, CH of CH_2), 2.05 (3H, s, NHAc), 2.12-2.26 (1H, m, CH of CH_2), 2.62-3.58 (11H, m, 5 of CH_2 and CH), 4.06 (2H, s, CH_2NH), 7.34-7.42 (4H, m, Ar-H), 7.52 (1H, d, J=8.6Hz, Ar-H), 7.61 (2H, d, J=8.4Hz, Ar-H), 7.90 (1H, d, J=2.0Hz, Ar-H), 9.05 (2H, s, Ar-H), 10.08 (1H, s, NH), 11.30 (1H, s, NH).

EXAMPLE 33

(3R)-3-(N-Benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. 0.5 Etherate.

Prepared from (3S)-N-[(R)-1-phenethyl]-3-(hydroxymethyl)pyrrolidine (*J. Med. Chem.*, 1990, 33 (1), 71) and Intermediate 3 using the procedures described for Examples 2 and 7. The 2.5 hydrogen oxalate 0.5 etherate salt was prepared, mp 230-232°C. (Found: C, 55.88; H, 6.02; N. 12.94. $C_{24}H_{28}N_6 \cdot 2.5(C_2H_2O_4) \cdot 0.5(Et_2O)$ requires C, 56.18; H, 5.78; N, 12.68%), m/e 401 $(M+1)^+$. δ (360MHz, D_6-DMSO) 1.70-1.84 (1H, m, CH of CH_2), 2.14-2.26 (1H, m, CH of CH_2), 2.68-3.60 (11H, m, 5 of CH_2 and CH), 4.13 (2H, s, CH_2Bn), 7.35-7.54 (8H, m, Ar-H), 7.90 (1H, s, Ar-H), 9.04 (2H, s, Ar-H), 11.30 (1H, s, NH).

EXAMPLE 34

(3S)-3-(4-(Pyridyl)methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 3.0 Hydrogen Oxalate. 0.7 Hydrate. 0.2 Etherate.

a) (3S)-N(H)-3-(4-(Pyridyl)methyl)aminomethyl pyrrolidine

Prepared from (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine and 4-aminomethyl pyridine using the procedures described for Example 5, parts b and c. δ (250MHz, D_4-MeOH) 1.33-1.46 (1H, m, CH of CH_2), 1.88-2.04 (1H, m, CH of CH_2),

2.21-3.05 (7H, m, 3 of CH_2 and CH), 3.83 (2H, s, CH_2-pyridyl), 7.42-7.45 (2H, m, Ar-H), 8.45-8.48 (2H, m, Ar-H).

b) (3S)-3-(4-(Pyridyl)methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 3.0 Hydrogen Oxalate. 0.7 Hydrate. 0.2 Etherate.

Prepared from Intermediate 3 and the preceding N(H)-pyrrolidine using the procedure described for Example 2. The 3.0 hydrogen oxalate 0.7 hydrate 0.2 etherate salt was prepared, mp 213-215° C. (Found: C, 51.00; H, 5.15; N, 13.73. $C_{23}H_{27}N_7 \cdot 3.0(C_2H_2O_4) \cdot 0.7\ H_2O \cdot 0.2(Et_2O)$ requires C, 51.20; H, 5.25; N, 14.03%); m/e 402 $(M+1)^+$. δ (360MHz, D_6-DMSO) 1.70-1.84 (1H, m, CH of CH_2), 2.14-2.26 (1H, m, CH of CH_2), 2.66-2.80 (1H, m, CH of CH_2), 2.94-3.62 (10H, m, 4 of CH_2 and 2 of CH), 4.12 (2H, s, CH_2-pyridyl), 7.36 (1H, dd, J=1.8 and 8.6Hz, Ar-H), 7.40 (1H, s, Ar-H), 7.49 (2H, d, J=5.7Hz, Ar-H), 7.53 (1H, d, J=8.6Hz, Ar-H), 7.90 (1H, d, J=1.8Hz, Ar-H), 8.61 (2H, d, J=5.7Hz, Ar-H), 9.04 (2H, s, Ar-H), 11.30 (1H, s, NH).

EXAMPLE 35

3-(N-Benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]azetidine. 2.0 Hydrogen Oxalate. Hemihydrate.

a) N-*tert*-Butyloxycarbonylazetidin-3-ol

A suspension of azetidin-3-ol hydrochloride (*J. Chem. Soc., Chem. Commun.*, 1968, 93; 18.4g, 168.1mmol), $(Boc)_2O$ (56g, 256.6 mmol) and NEt_3 (52ml, 373mmol), in anhydrous THF (1000ml) was stirred at room temperature for 16h. The solvent was removed under vacuum and the residue partitioned between EtOAc (260ml) and H_2O (200ml). The aqueous was further extracted with EtOAc (3 x 200ml). The combined extracted were dried (Na_2SO_4) and evaporated and the crude product was

chromatographed on silica gel eluting with CH_2Cl_2/MeOH (95:5→90:10) to give the title product (16.9g, 58%). δ (250MHz, $CDCl_3$) 1.43 (9H, s, $(Me)_3$), 3.28 (1H, br s, OH), 3.77-3.83 (2H, m, CH_2), 4.10-4.17 (2H, m, CH_2), 4.50-4.62 (1H, m, CH).

b) N-*tert*-Butyloxycarbonyl-3-cyanoazetidine

Methane sulphonyl chloride (4.7ml, 60mmol) was added slowly to a stirred solution of the preceding alcohol (7.0g, 40mmol) in dry pyridine (40ml) at +20°C. The mixture was stirred for 4h and the solvent then removed under vacuum. The residue was partitioned between EtOAc/H_2O and the aqueous was extracted with EtOAc (x2). The combined extracts were dried (Na_2SO_4) and evaporated to give the desired mesylate (10.2g, 100%). A mixture of the mesylate (2.5g, 10mmol) and tetra-*n*-butylammonium cyanide (8.0g, 30mmol), in anhydrous toluene (80ml) was heated at reflux for 64h. The mixture was cooled to room temperature and partitioned between EtOAc/H_2O. The aqueous was extracted with EtOAc (x2), the combined extracts dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel eluting with 40% EtOAc/petroleum ether to give the title nitrile (1.15g, 80%). δ (250MHz, $CDCl_3$) 1.45 (9H, s $(Me)_3$), 3.33-3.46 (1H, m, CH), 4.11-4.25 (4H, m, 2 of CH_2).

c) N-*tert*-Butyloxycarbonyl-3-formylazetidine

Diisobutyl aluminium hydride (39.8ml of a 1.0M solution in toluene, 39.8mmol) was added slowly to a stirred solution of the preceding nitrile (3.63g, 19.9mmol), in anhydrous THF (100ml), at 0°C. The mixture was allowed to warm to room temperature and stir for 2h. The reaction was quenched by addition of EtOAc (40ml) and aqueous NH_4Cl (40ml) and partitioned between EtOAc/H_2O. The aqueous was further extracted with EtOAc (x3) and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel eluting with 65% EtOAc/petroleum ether to give the desired aldehyde

(1.35g, 37%). δ (250MHz, $CDCl_3$) 1.45 (9H, s, $(Me)_3$), 3.30-3.42 (1H, m, CH), 4.05-4.17 (4H, m, 2 of CH_2), 9.85 (1H, d, J=2.1Hz, CHO).

d) N-(1H)-3-(Benzylamino)methyl azetidine

Sodium cyanoborohydride (1.15g, 18.3mmol) was added to a solution of benzylamine (1.04ml, 9.5mmol) and glacial acetic acid (2.10ml, 36.7mmol), in dry methanol (150ml), at room temperature. The solution was cooled to 0°C and a solution of the preceding aldehyde (1.35g, 7.3mmol), in methanol (50ml), was added. The mixture was warmed to room temperature and stirred for 20h. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc/aq. K_2CO_3. The aqueous was extracted with EtOAc (x3) and the combined extracts dried and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (95:5→92:8) to give the desired N-benzylaminoazetidine (1.5g, 73%). A mixture of formic acid (99%, 18ml) and H_2O (2ml) was added to N-*tert*-butyloxycarbonyl-3-(benzylamino)methyl azetidine (1.5g, 5.3mmol) at 0°C. The mixture was warmed to room temperature, stirred for 16h, and the solvent then removed under vacuum. Saturated aqueous K_2CO_3 (25ml) was added to the residue and extracted with "BuOH (5 x 25ml). The combined extracts were evaporated and the residue treated with CH_2Cl_2 (50ml) and filtered to remove inorganics. The filtrate was dried (Na_2SO_4) and evaporated to give the *title compound* (0.512g, 55%). δ (360MHz, $CDCl_3$) 2.85 (2H, s, CH_2Ph), 3.36-3.39 (1H, m, CH), 3.57-3.72 (4H, m, 2 of CH_2), 3.79 (2H, s, CH_2), 7.23-7.34 (5H, m, Ar-H).

e) 3-(N-Benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]azetidine. 2.0 Hydrogen Oxalate. Hemihydrate.

Methane sulphonyl chloride (360μL, 4.65mmol) was added to a stirred suspension of 2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethyl alcohol (Intermediate 3; 0.7g, 3.07mmol) in dry pyridine (17ml), at -20°C. The mixture was stirred at this temperature for 0.25h and then warmed to

room temperature and stirred for 16h. The reaction mixture was quenched by addition of H_2O (50ml) and then extracted with EtOAc (50ml) and CH_2Cl_2 (2 x 50ml). The combined extracts were dried (Na_2SO_4) and evaporated and the residue purified by chromatography on silica gel eluting with CH_2Cl_2/MeOH (9:1) to give the desired mesylate (0.59g, 63%). The mesylate (0.39g, 1.2mmol) was added to a stirred suspension of N-(1H)-3-(benzylamino) methylazetidine (0.269g, 1.53mmol), K_2CO_3 (0.49g, 3.55mmol) and NaI (0.18g, 1.20mmol), in IPA (40ml). The mixture was heated at reflux for 18h, cooled to room temperature and the solvent removed *in vacuo*. The residue was partitioned between CH_2Cl_2/H_2O and the aqueous further extracted with CH_2Cl_2 (x3). The combined extracts were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (50:8:1) to give the title product (0.135g, 27%). The 2.0 hydrogen oxalate hemihydrate salt was prepared, mp 156-158°C. Found: C, 55.98; H, 5.50; N, 14.40. $C_{23}H_{28}N_6 \cdot 2(C_2H_2O_4) \cdot 0.5\ H_2O$ requires C, 56.34; H, 5.43; N, 14.60%); m/e 387 $(M+1)^+$.
δ (360MHz, D_6-DMSO) 2.80-3.22 (5H, m, 2 of CH_2 and CH), 3.36-3.44 (2H, m, CH_2), 3.76-3.86 (2H, m, CH_2), 3.98-4.08 (4H, m, 2 of CH_2), 7.28-7.48 (7H, m, Ar-H), 7.52 (1H, d, J=8.7Hz, Ar-H), 7.89 (1H, d, J=1.8Hz, Ar-H), 9.04 (2H, s, Ar-H), 11.31 (1H, s, NH).

EXAMPLE 36

4-Benzyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperidine. Hydrogen Oxalate.

a) 3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propan-1-ol

A solution of 4'-(1,2,4-triazol-4-yl)phenylhydrazine (25g, 143mmol) in dioxan (250ml) was treated with dihydropyran (24g, 286mmol) followed by 1M hydrochloric acid (150ml) and heated at reflux for 18h. The reaction mixture was evaporated, treated with toluene then re-evaporated.

Inorganic solids were removed by treating the residue with a mixture of methanol and acetonitrile. The mother liquors were purified by column chromatography on silica using dichloromethane/methanol (9:1→4:1) as the eluant. The compound was recrystallised from acetonitrile to afford the *title compound* as a colourless solid (10.24g, 30%); mp 205-207°C. (Found: C, 64.37; H, 5.76; N, 22.83. $C_{15}H_{14}N_4O$ requires C, 64.45; H, 5.82; N, 23.13%.) δ (360MHz, d_6-DMSO) 1.81 (2H, q, J=7Hz, CH_2), 2.75 (2H, t, J=8Hz, CH_2), 3.46 (2H, dt, J_1=6, J_2=5Hz, CH_2), 4.43 (1H, t, J=5Hz, OH), 7.26 (1H, d, J=2Hz, Ar-H), 7.29 (1H, dd, J_1=9, J_2=2Hz, Ar-H), 7.47 (1H, d, J=9Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.05 (1H, br s, indole NH). MS, CI^+, m/z=243 for $(M+H)^+$.

b) 4-Benzyl-4-hydroxy-1[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]piperidine. Hydrogen Oxalate.

A fine suspension of the preceding indole (300mg, 1.24mmol), stirred under a nitrogen atmosphere in anhydrous tetrahydrofuran (30ml) was treated with triethylamine (0.35ml, 2.48mmol) followed by methanesulphonyl chloride (0.2ml, 2.48mmol). The reaction mixture was stirred at ambient temperature for 1.5h, filtered, then evaporated to dryness. The residue was partitioned between dichloromethane (40ml) and water (30ml). The organic layer was separated, washed with water (30ml), then dried (sodium sulphate) and evaporated to dryness to give the mesylate as a dark yellow semi-solid. The mesylate was dissolved in propan-2-ol (70ml) then treated with potassium carbonate (514mg, 3.72mmol) and 4-benzyl-4-hydroxypiperidine (712mg, 3.72mmol) and heated at reflux, with stirring, for 24 hours. The reaction mixture was evaporated to dryness, the residue partitioned between dichloromethane (50ml) and water (30ml). The organic layer was separated, washed with water (30ml), dried (potassium carbonate) then evaporated to give an orange gum which was purified by column chromatography on silica using dichloromethane/methanol/ammonia (20:1:0.1 to 8:1:0.1) to afford the title

product free base as a viscous colourless gum (302mg, 59%). The hydrogen oxalate salt had mp 117-119°C (propan-2-ol/ethanol (2:1)). (Found: C, 62.05; H, 6.22; N, 12.17. $C_{28}H_{28}N_6O \cdot 1.3(C_2H_2O_4) \cdot 0.4(CH_3)_2CHOH$ requires C, 62.15; H, 6.30; N, 12.58%.) δ (360MHz, d_6-DMSO) 1.55 (2H, d, J=12Hz, CH_2), 1.74 (2H, dd, $J_1=J_2=12Hz$, CH_2), 1.98-2.05 (2H, m, CH_2), 2.72-2.75 (4H, m, $\underline{CH_2}$-indole and $\underline{CH_2}$-phenyl), 2.96-3.10 (4H, m, 2 x CH_2), 3.20-3.32 (2H, m, CH_2), 7.20-7.33 (7H, m, Ar-H), 7.49 (1H, d, J=8Hz, Ar-H), 7.79 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.19 (1H, s, indole-NH); MS, ES^+, m/e=416 for $(M+H)^+$ of free base.

EXAMPLE 37

3-(N-Benzyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl]azetidine. 2.0 Hydrogen Oxalate. 0.1 Etherate. Monohydrate.

Prepared from 3-(5-[1,2,4-triazol-4-yl]-1H-indol-3-yl)propan-1-ol and N-(1H)-3-(benzylamino)methyl azetidine as exemplified for Example 35. The 2.0 hydrogen oxalate 0.1 etherate monohydrate salt was prepared, mp 151-154°C. (Found: C, 56.61; H, 6.06; N, 13.57. $C_{24}H_{28}N_6 \cdot 2(C_2H_2O_4) \cdot 0.1(Et_2O) \cdot 1.0\ H_2O$ requires C, 56.29; H, 5.82; N, 13.87%), m/e 401 $(M+1)^+$. δ (360MHz, d_6-DMSO) 1.74-1.88 (2H, m, CH_2), 2.75 (2H, t, J=7.5Hz, CH_2), 2.98-3.14 (5H, m, CH and 2 of CH_2), 3.77 (2H, t, J=7.5Hz, CH_2), 3.96-4.06 (4H, m, 2 of CH_2), 7.31-7.44 (7H, m, Ar-H), 7.50 (1H, d, J=8.5Hz, Ar-H), 7.80 (1H, d, J=1.6Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.18 (1H, s, NH).

EXAMPLE 38

4-(Benzylamino)methyl-4-hydroxy-1-[3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperidine

a) 1-Benzyl-4-hydroxy-4-(*tert*-butyloxycarbonylamino)methyl piperidine

To a stirred solution of 4-aminomethyl-1-benzyl-4-hydroxy piperidine (*Synth. Commun.*, 1994, 24 (10), 1483) (11g, 50mmol) in dichloromethane (300ml) was added di-*tert*-butyldicarbonate (11g, 50mmol). The solution was stirred overnight at ambient temperature, and then quenched with 10% aqueous potassium carbonate (150ml). The organic layer was decanted, dried (sodium sulphate) and evaporated under high vacuum. The residue was purified by column chromatography on silica, using dichloromethane/methanol as eluant, to afford the *title compound* (11.6g, 70%), mp 109-112°C. δ (250MHz, d_6-DMSO) 1.16-1.47 (4H, m, 2 of CH_2), 1.27 (9H, s, $OC(Me)_3$), 2.09-2.26 (2H, m, CH_2), 2.29-2.44 (2H, m, CH_2), 2.80 (2H, d, J=6Hz, CH_2), 3.25 (2H, s, CH_2), 4.09 (1H, s, OH), 6.49 (1H, t, J=6Hz, NH), 7.08-7.26 (5H, m, Ar-H). MS, m/e=321 for $(M+H)^+$.

b) 4-Hydroxy-4-(*tert*-butyloxycarbonylamino)methyl piperidine

To a solution of the foregoing amine (12.5g, 39mmol) in methanol (300ml) was added 10% palladium on carbon (2.5g) in methanol (20ml), and ammonium formate (7g, 11mmol). The suspension was stirred at ambient temperature for 3h, then the catalyst filtered off and washed with methanol. The solvent was evaporated *in vacuo* and the residue triturated with dichloromethane. The resulting solid was dissolved in saturated aqueous potassium carbonate and extracted with dichloromethane (12x). The combined organics were dried (sodium sulphate) and evaporated to give the required product as a solid (7g, 78%) mp 136-138°C. δ (360MHz, d_6-DMSO) 1.22-1.48 (4H, m, 2 of CH_2), 1.38 (9H, s, $OC(Me)_3$), 2.52-2.62 (2H, m, CH_2), 2.62-2.76 (2H, m, CH_2), 2.88 (2H, d, J=6Hz, CH_2), 4.12 (1H, s, OH), 6.49 (1H, t, J=6Hz, NH). MS, m/e=231 for $(M+H)^+$.

c) 4-(*tert*-Butyloxycarbonylamino)methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl piperidine

The *title compound* was obtained (2.7g, 60%) from the compounds in steps a and b, as described in Example 36; mp 86°C (sintered). (Found: C, 60.43; H, 7.79; N, 16.95. $C_{24}H_{34}N_6O_3 \cdot H_2O \cdot 0.4(CH_3OH)$ requires C, 60.33; H, 7.81; N, 17.31%. δ (250MHz, d_6-DMSO) 1.26-1.56 (4H, m, 2 of CH_2), 1.37 (9H, s, $OC(Me)_3$), 1.72-1.90 (2H, m, CH_2), 2.14-2.54 (6H, m, 3 of CH_2), 2.70 (2H, t, J=7Hz, CH_2), 2.89 (2H, d, J=6Hz, CH_2), 4.15 (1H, s, OH), 6.56 (1H, br t, NH), 7.25-7.32 (2H, m, Ar-H), 7.47 (1H, d, J=8Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.08 (1H, s, NH); MS; m/e=455 for $(M+H)^+$.

d) 4-Aminomethyl-4-hydroxy-1-[3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperidine

To a solution of the preceding product (2.5g, 5.5mmol) in dichloromethane (50ml) was added trifluoroacetic acid (4.2ml, 55mmol). The mixture was stirred overnight at ambient temperature then further trifluoroacetic acid (4.2ml, 55mmol) was added and the mixture stirred 1.5 hours at 35°C. The solvent and excess reagent were evaporated *in vacuo*, and the residue dissolved in a minimum of methanol and washed with diethyl ether (2 x 10ml). The methanol was evaporated *in vacuo* and the residue partitioned between 10% aqueous potassium carbonate and *n*-butanol. The aqueous was re-extracted with *n*-butanol (3x). The combined organics were evaporated to dryness and the low melting solid used crude in the next reaction. MS, m/e=355 for $(M+H)^+$. δ (250MHz, d_6-DMSO) 1.32-1.50 (4H, m, 2 of CH_2), 1.72-1.88 (2H, m, CH_2), 2.17-2.36 (4H, m, 2 of CH_2), 2.36-2.55 (2H, m, CH_2), 2.34 (2H, s, CH_2), 2.70 (2H, t, J=7Hz, CH_2), 7.24-7.32 (2H, m, Ar-H), 7.48 (1H, d, J=8Hz, Ar-H), 7.78 (1H, d, J=2Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.21 (1H, s, NH).

e) 4-(Benzylamino)methyl-4-hydroxy-1-[3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperidine

To a stirred solution of the foregoing amine (400mg, 1.1mmol) in methanol (10ml) was added benzaldehyde (100µl, 1mmol), glacial acetic acid (100µl, 1.7mmol) and sodium cyanoborohydride (69mg, 1.1mmol). The yellow solution was stirred overnight at room temperature, then 10% aqueous potassium carbonate (5ml) was added. The mixture was evaporated *in vacuo* and the residue partitioned between 10% aqueous potassium carabonate and *n*-butanol. The aqueous was re-extracted once with *n*-butanol. The combined organics were evaporated to dryness to give a foam which was purified by column chromatography on silica using dichloromethane/methanol/ammonia as eluant, to afford the *title compound* (200mg, 41%); mp>60°C (sintered). (Found: C, 67.55; H, 7.04; N, 17.75. $C_{28}H_{37}N_6O \cdot H_2O$ requires C, 67.51; H, 7.41; N, 18.17%. δ (360MHz, d_6-DMSO) 1.40-1.58 (4H, m, 2 of CH_2), 1.74-1.86 (2H, m, CH_2), 2.20-2.55 (6H, m, 3 of CH_2), 2.39 (2H, s, CH_2), 2.70 (2H, t, J=7Hz, CH_2), 3.71 (2H, s, CH_2), 4.01 (1H, s, OH), 7.17-7.32 (7H, m, Ar-H), 7.46 (1H, d, J=8Hz, Ar-H), 7.76 (1H, d, J=2Hz, Ar-H), 9.00 (2H, s, Ar-H), 11.05 (1H, s, NH). MS, m/e=445 for $(M+H)^+$.

EXAMPLE 39

4-[(N-Benzyl-N-methyl)amino]methyl-4-hydroxy-1-[3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperidine. 2.0 Hydrogen Oxalate.

To a solution of 4-(benzylamino)methyl-4-hydroxy-1-[3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperidine (150mg, 0.34mmol) in methanol (8ml) were added 38% in water formaldehyde (27µl, 0.37mmol), glacial acetic acid (85µl, 1.48mmol) and sodium cyanoborohydride (23mg, 0.37mmol). The solution was stirred overnight at room temperature, the 10% aqueous potassium carbonate (5ml) was added. The mixture was evaporated to dryness and the residue partitioned between 10% aqueous

potassium carbonate and dichloromethane. The aqueous was re-extracted with dichloromethane (3x). The combined organics were dried (sodium sulphate) and evaporated to give the required product (130mg, 83%). The oxalate salt had mp>132°C (sintered). (Found: C, 57.17; H, 6.17; N, 12.59. $C_{27}H_{34}N_6O \cdot 2(CO_2H)_2 \cdot 0.75\ H_2O$ requires C, 57.09; H, 6.10; N, 12.89%.) δ (360MHz, d_6-DMSO) 1.64-1.86 (4H, m, 2 of CH_2), 1.98-2.12 (2H, m, CH_2), 2.31 (3H, s, CH_3), 2.5 (2H, s, CH_2), 2.76 (2H, br t, CH_2), 3.0-3.17 (4H, m, 2 of CH_2), 3.23-3.40 (2H, m, CH_2), 3.68 (2H, s, CH_2), 7.20-7.40 (7H, m, Ar-H), 7.50 (1H, d, J=8Hz, Ar-H), 7.80 (1H, d, J=2Hz, Ar-H), 9.02 (2H, s, Ar-H), 11.19 (1H, s, NH). MS, m/e=459 for $(M+H)^+$.

EXAMPLE 40

3-(N-Benzyl-N-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]azetidine, 1.5 Hydrogen Oxalate, 1.5 Hydrate.

The *title compound* was prepared from Example 35 and formaldehyde using the general reductive amination procedure. The 1.5 hydrogen oxalate 1.5 hydrate salt was prepared, mp 125-131°C. (Found: C, 56.78; H, 6.15, N, 14.13. $C_{24}H_{28}N_6 \cdot 1.5(C_2H_2O_4) \cdot 1.5\ H_2O$ requires C, 56.48; H, 5.94; N, 14.36%, m/e 401 $(M+1)^+$. δ (360MHz, d_6-DMSO) 2.13 (3H, s, Me), 2.71 (2H, d, J=7.6Hz, CH_2NMe), 2.90-3.08 (3H, m, CH and CH_2), 3.36-3.46 (2H, m, CH_2), 3.54 (2H, s, CH_2Ph), 3.77 (2H, t, J=7.5Hz, CH_2), 4.09 (2H, t, J=7.5Hz, CH_2), 7.22-7.40 (7H, m, Ar-H), 7.53 (1H, d, J=8.7Hz, Ar-H), 7.88 (1H, s, Ar-H), 9.03 (2H, s, Ar-H), 11.29 (1H, s, NH).

EXAMPLE 41

(3S)-3-(N-[R]-α-Methylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.5 Hydrogen Oxalate, 0.5 Hydrate, 0.2 Diethyl etherate.

a) (3S)-N(H)-3-(N-[R]-α-Methylbenzyl)amino methyl pyrrolidine

Prepared from (3R)-N-*tert*-butyloxycarbonyl-3-(methylsulphonyloxymethyl)pyrrolidine and (R)-α-methyl benzylamine using the procedures described for Example 5, parts b and c.

b) (3S)-3-(N-[R]-α-Methylbenzyl)aminomethyl-1-[2-(5-1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. 0.5Hydrate. 0.2 Diethyl etherate.

Methane sulphonyl chloride (1.44g, 12.6mmol) was added to a stirred suspension of Intermediate 3 (1.91g, 8.4mmol) in anhydrous pyridine (60ml), at -20°C. The mixture was warmed to room temperature and stirred for 2h. The pyridine was removed *in vacuo*, water (100ml) added and the mixture extracted with CH_2Cl_2 (3 x 75ml). The combined extracts were dried ($MgSO_4$), the solvent removed under vacuum and the residue chromatographed on silica gel eluting with MeOH/CH_2Cl_2 (9:1) to give the desired mesylate (1.50g, 60%). A mixture of the preceding mesylate (0.308g, 1.0mmol), (3S)-N(H)-3-(N-[R]-α-methylbenzyl)aminomethyl pyrrolidine (0.35g, 1.71mmol) and K_2CO_3 (0.414g, 3.0mmol), in IPA (25ml), was heated at reflux for 4h. The solvent was removed *in vacuo* and the residue taken up into CH_2Cl_2 and washed with H_2O (x3). The organic was dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (80:8:1) to afford the title product (0.206g, 50%). The 2.5 hydrogen oxalate 0.5 hydrate 0.2 diethyl etherate salt was prepared, mp 192-194°C; (Found: C, 55.61; H, 5.84; N, 12.68. $C_{25}H_{30}N_6 \cdot 2.5(C_2H_2O_4) \cdot 0.5\ H_2O \cdot 0.2(Et_2O)$ requires C, 55.76; H, 5.77; N, 12.67%), m/e 415 $(M+1)^+$.

EXAMPLE 42

(3S)-3-(N-[S]-α-Methylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate 0.6Hydrate 0.1 Diethyl etherate

Prepared from Intermediate 3 as described for Example 41, mp 191-193°C, (Found: C, 55.31; H, 5.69; N, 12.54. $C_{25}H_{30}N_6 \cdot 2.5(C_2H_2O_4) \cdot 0.6\ H_2O \cdot 0.1(Et_2O)$ requires C, 55.65; H, 5.68; N, 12.81%), m/e 415 $(M+1)^+$.

EXAMPLE 43

(3S)-3-(N-Furan-3-ylmethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. 0.65 Diethyl etherate.

a) (3S)-N(H)-3-(N-Furan-3-ylmethyl)aminomethyl pyrrolidine

Prepared from (3R)-N-*tert*-butyloxycarbonyl-3-(methylsulphonyloxymethyl)pyrrolidine and 3-furanmethylamine using the procedures described for Example 5, parts b and c.

b) (3S)-3-(N-Furan-3-ylmethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. 0.65 Diethyl etherate.

Prepared from Intermediate 3 and the preceding pyrrolidine as described for Example 41, (Found: C, 53.81; H, 5.97; N, 12.69. $C_{22}H_{26}NO_6 \cdot 2.5(C_2H_2O_4) \cdot 0.65(Et_2O)$ requires C, 53.56; H, 5.69, N, 12.66%). δ (360MHz, d_6-DMSO) 1.70-1.84 (1H, m, CH of CH_2), 2.14-2.26 (1H, m, CH of CH_2), 2.68-2.80 (1H, m, CH), 2.94-3.24 (5H, m, 2 of CH_2 and CH of CH_2), 3.26-3.58 (5H, m, 2 of CH_2), 4.02 (2H, s, CH_2), 6.65 (1H, s, Ar-H), 7.37 (1H, dd, J=2.1 and 8.7Hz, Ar-H), 7.40 (1H, s, Ar-H), 7.53 (1H, d, J=8.7Hz, Ar-H), 7.72 (1H, s, Ar-H), 7.81 (1H, s, Ar-H), 7.91 (1H, d, J=2.1Hz, Ar-H), 9.05 (2H, s, Ar-H), 11.31 (1H, s, NH).

EXAMPLE 44

(3S)-3-(N-Furan-2-ylmethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. 0.5 Hydrate.

Prepared as described for Example 43, (Found: C, 51.92; H, 5.28; N, 13.32. $C_{22}H_{28}N_8O \cdot 2.5(C_2H_2O_4) \cdot 0.5\ H_2O$ requires C, 51.92; H, 5.16; N, 13.46%). δ (360MHz, d_6-DMSO) 1.70-1.84 (1H, m, CH of CH_2), 2.12-2.24 (1H, m, CH of CH_2), 2.64-2.78 (1H, m, CH), 2.98 (2H, d, J=6.8Hz, CH_2), 3.04-3.58 (8H, m, 4 of CH_2), 4.16 (2H, s, CH_2), 6.51 (1H, dd, J=3.2 and 1.6Hz, Ar-H), 6.57 (1H, d, J=3.2Hz, Ar-H), 7.36 (1H, dd, J=2.1 and 8.7Hz, Ar-H), 7.40 (1H, s, Ar-H), 7.52 (1H, d, J=8.7Hz, Ar-H), 7.74 (1H, d, J=1.6Hz, Ar-H), 7.90 (1H, s, Ar-H), 9.04 (2H, s, Ar-H), 11.31 (1H, s, NH).

EXAMPLE 45

(3S)-3-[N-(R)-α-(Hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.4 Hydrogen Oxalate. 0.1 Hydrate.

1. (3S)-N(H)-3-[(R)-α-(Hydroxymethyl)benzyl]aminomethylpyrrolidine

a) (3S)-N-*tert*-Butyloxycarbonyl-3-(R)-α(hydroxymethyl)benzyl aminomethylpyrrolidine

A solution of (R)-(-)-phenylglycinol (2.20g, 16.1mmol) and (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine (1.0g, 3.58mmol), in toluene (20ml), was heated at 150°C for 6h in sealed pressure tube (Aldrich). The solvent was then removed under vacuum and the residue taken up into ethyl acetate (200ml) and washed with water (x4). The organic was dried ($MgSO_4$) and evaporated and the crude product chromatographed on silica gel eluting with CH_2Cl_2/MeOH (97:3)

to give the title-α-(hydroxymethyl)benzylaminomethylpyrrolidine (1.0g, 87%), δ (360MHz, $CDCl_3$) 1.45 (9H, s, $OC(Me)_3$), 1.52-2.60 (5H, m, CH_2 and CH), 2.90-3.76 (7H, m, 3 of CH_2 and CH), 7.25-7.39 (5H, m, Ar-H).

b) (3S)-N(H)-3-[(R)-α-Hydroxymethyl)benzyl]aminomethylpyrrolidine

Prepared from the preceding N-Boc pyrrolidine using the procedure described for Example 5, part c, δ (250MHz, $CDCl_3$) 1.25-1.45 (1H, m, CH of CH_2), 1.83-1.97 (1H, m, CH of CH_2), 2.14-2.61 (4H, m, 2 of CH_2), 2.80-3.09 (3H, m, CH_2 and CH), 3.46-3.76 (3H, m, CH_2 and CH), 7.25-7.38 (5H, m, Ar-H).

2. (3S)-3-[N-(R)-α-(Hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2,4 Hydrogen Oxalate. 0.1 Hydrate

Prepared from Intermediate 3 and the preceding pyrrolidine using the procedure described for Example 41, mp 158°C, (Found: C, 55.11; H, 5.58; N, 12.85. $C_{25}H_{30}N_6O \cdot 2.4(C_2H_2O_4) \cdot 0.1H_2O$ requires C, 55.20; H, 5.44; N, 12.96%), m/e 431 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.64-1.76 (1H, m, CH of CH_2), 2.12-2.24 (1H, m, CH of CH_2), 2.64-2.76 (2H, m, CH_2), 2.88-2.94 (1H, m, CH), 3.04-3.14 (3H, m, CH_2 and CH of CH_2), 3.30-3.42 (3H, m, CH_2 and CH of CH_2), 3.46-3.56 (1H, m, CH of CH_2), 3.73 (2H, d, J=5.7Hz, CH_2), 4.12-4.16 (2H, m, CH_2), 7.34-7.54 (8H, m, Ar-H), 7.90 (1H, s, Ar-H), 9.04 (2H, s, Ar-H), 11.31 (1H, s, NH).

EXAMPLE 46

(3S)-3-[N-(S)-α-(Hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2,4 Hydrogen Oxalate. 0.1 Hydrate.

a) (3S)-N(H)-3-[(S)-α-(Hydroxymethyl)benzyl]aminomethylpyrrolidine

Prepared from (S)-(+)-phenylglycinol and (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine using the procedures described for Example 45, part 1a.

b) (3S)-3-[N-(S)-α-(Hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.4 Hydrogen Oxalate. 0.1 Hydrate.

Prepared from Intermediate 3 and the preceding pyrrolidine using the procedure described for Example 41, mp 155°C, (Found: C, 55.35; H, 5.71; N, 12.82. $C_{25}H_{30}N_6O \cdot 2.4(C_2H_2O_4) \cdot 0.1\ H_2O$ requires C, 55.20; H, 5.44; N, 12.96%), m/e 431 $(M+1)^+$.

EXAMPLE 47

(3S)-3-[N-Benzyl-N-(2-hydroxy)ethyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.4 Hydrogen Oxalate.

a) (3S)-N(H)-3-[N-Benzyl-N-(2-hydroxy)ethyl]aminomethylpyrrolidine

Prepared from N-benzylethanolamine and (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine using the procedures described for Example 5, parts b and c, δ (250MHz, $CDCl_3$) 1.24-1.60 (2H, m, CH_2), 1.82-1.94 (2H, m, CH_2), 2.26-3.06 (9H, m, 4 of CH_2 and CH), 3.56-3.60 (2H, m, CH_2), 7.20-7.36 (5H, m, Ar-H).

b) (3S)-3-[N-Benzyl-N-(2-hydroxy)ethyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.4 Hydrogen Oxalate.

Prepared from Intermediate 3 and the preceding pyrrolidine using the procedure described for Example 41, mp 117°C, (Found: C, 55.93; H, 5.39; N, 12.50. $C_{26}H_{32}N_6O \cdot 2.4(C_2H_2O_4)$ requires C, 55.99; H, 5.61; N, 12.72%), m/e 445 $(M+1)^+$, δ(360MHz, D_6-DMSO) 1.56-1.70 (1H, m, CH of CH_2), 2.04-2.16 (1H, m, CH of CH_2), 2.52-2.68 (7H, m, 3 of CH_2 and CH),

3.04-3.12 (2H, m, CH_2), 3.28-3.52 (6H, m, 3 of CH_2), 3.68 (2H, ABq, J=14Hz, CH_2), 7.20-7.34 (5H, m, Ar-H), 7.38 (1H, dd, J=8.6 and 1.5Hz, Ar-H), 7.53 (1H, d, J=8.6Hz, Ar-H), 7.89 (1H, d, J=1.5Hz, Ar-H), 9.03 (2H, s, Ar-H), 11.31 (1H, s, NH).

EXAMPLE 48

(3S)-3-(N-Phenethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5Hydrogen Oxalate. Hemihydrate.

a) (3S)-N-(H)-3-(N-Phenethyl)aminomethylpyrrolidine

Prepared from phenethylamine and (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine using the procedures described for Example 5, parts b and c.

b) (3S)-3-(N-Phenethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. Hemihydrate.

Prepared from the preceding pyrrolidine and Intermediate 3 using the procedure described for Example 41, mp 189-190°C, (Found: C, 55.59; H, 5.55; N, 12.85. $C_{28}H_{30}N_6 \cdot 2.5(C_2H_2O_4) \cdot H_2O$ requires C, 55.55; H, 5.59; N, 12.96%), m/e 415 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.74-1.86 (1H, m, CH of CH_2), 2.14-2.26 (1H, m, CH of CH_2), 2.68-3.60 (15H, m, CH and 7 of CH_2), 7.22-7.40 (7H, m, Ar-H), 7.53 (1H, d, J=8.6Hz, Ar-H), 7.92 (1H, d, J=1.5Hz, Ar-H), 9.05 (2H, s, Ar-H), 11.30 (1H, s, NH).

EXAMPLE 49

(3S)-3-(N-Phenethyl-N-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. 0.1 Diethyl etherate.

a) (3S)-N(H)-3-(N-Phenethyl-N-methyl)aminomethylpyrrolidine

Prepared from N-phenethyl-N-methylamine and (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethyl pyrrolidine using the procedures described for Example 5, parts b and c.

b) (3S)-3-(N-Phenethyl-N-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.5 Hydrogen Oxalate, 0.1 Diethyl etherate.

Prepared from the preceding pyrrolidine and Intermediate 3 using the procedure described for Example 41, mp 168-170°C, (Found: C, 57.02; H, 5.71; N, 12.78. $C_{26}H_{32}N_6 \cdot 2.5(C_2H_2O_4) \cdot 0.1$(Diethyl ether) requires C, 57.05; H, 5.79; N, 12.71%), m/e 429 $(M+1)^+$.

EXAMPLE 50

(3S)-3-(N-α-Dimethylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.45 Hydrogen Oxalate, 0.1 Diethyl etherate.

Prepared from Intermediate 3 and (3R)-N-*tert*-butyloxycarbonyl-3-methylsulphonyloxymethylpyrrolidine using the general procedures, mp 172-174°C, (Found: C, 57.15; H, 5.94; N, 13.14. $C_{26}N_{32}N_6 \cdot 2.45(C_2H_2O_4) \cdot$ 0.1(Diethyl ether) requires C, 57.26; H, 5.82; N, 12.80%), m/e 429 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.61 (6H, s, 2 of CH_3), 1.61-1.70 (1H, m, CH of CH_2), 2.10-2.21 (1H, m, CH of CH_2), 2.54-2.62 (3H, m, CH_2 and CH), 2.96-3.48 (8H, m, 4 of CH_2), 7.30-7.57 (8H, m, Ar-H), 7.84 (1H, d, J=1.8Hz, Ar-H), 8.92 (2H, s, Ar-H), 11.12 (1H, s, NH).

EXAMPLE 51

(3S)-3-(N-[S]-α-Methylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.5 Hydrogen Oxalate, 0.2 Hydrate.

a) 2-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]ethyl alcohol

Prepared from 4-(1,2,4-triazol-1-yl)aniline (EP497512) as described for Intermediate 3, δ (250MHz, D_6-DMSO) 2.89 (2H, t, J=7.2Hz, CH_2), 3.64-3.74 (2H, m, CH_2), 4.67 (1H, t, J=5.3Hz, OH), 7.29 (1H, d, J=2.3Hz, Ar-H), 7.47 (1H, dd, J=8.7 and 1.5Hz, Ar-H), 7.53 (1H, dd, J=8.7 and 2.3Hz, Ar-H), 7.95 (1H, d, J=1.9Hz, Ar-H), 8.19 (1H, s, Ar-H), 9.19 (1H, s, Ar-H), 11.10 (1H, s, NH).

b) (3S)-3-(N-[S]-α-Methylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.5 Hydrogen Oxalate. 0.2 Hydrate

Prepared from 2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethyl alcohol and (3S)-N(H)-3-(N-[S]-α-methylbenzyl)aminomethyl pyrrolidine as described for Example 41, mp 203-204°C, (Found: C, 55.95; H, 5.51; N, 13.11. $C_{25}H_{30}N_6 \cdot 2.5(C_2H_2O_4) \cdot 0.2\ H_2O$ requires C, 56.02; H, 5.55; N, 13.07%), m/e 415 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.54 (3H, d, J=6.7Hz, CH_3), 1.60-1.74 (1H, m, CH of CH_2), 2.11-2.22 (1H, m, CH of CH_2), 2.60-3.56 (10H, m, 4 of CH_2 and 2 of CH of CH_2), 4.24-4.30 (2H, m, CH_2), 7.34-7.56 (8H, m, Ar-H), 8.03 (1H, s, Ar-H), 8.19 (1H, s, Ar-H), 9.19 (1H, s, Ar-H), 11.28 (1H, s, NH).

EXAMPLE 52

(3S)-3-[N-[R]-α(Hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.0 Hydrogen Oxalate. 0.3 Hydrate.

Prepared from 2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethyl alcohol and (3S)-N(H)-3-[(R)-α-(hydroxymethyl)benzyl]aminomethyl pyrrolidine using the procedures described for Example 41, mp 173-174°C, (Found: C, 56.57; H, 5.77; N, 13.57. $C_{25}H_{30}N_6O \cdot 2.0(C_2H_2O_4) \cdot 0.3\ H_2O$ requires C, 56.54; H, 5.66; N, 13.64%), m/e 431 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.62-1.76 (1H, m, CH of CH_2), 2.10-2.22 (1H, m, CH of CH_2), 2.56-2.72 (2H, m, CH and CH of CH_2), 2.80-2.90 (1H, m, CH of CH_2), 3.02-3.52 (7H, m, 3 of CH_2 and CH), 3.64-3.70 (2H, m, CH_2), 4.02-4.06 (2H, m, CH_2), 7.32-

7.57 (8H, m, Ar-H), 8.03 (1H, s, Ar-H), 8.20 (1H, s, Ar-H), 9.18 (1H, s, Ar-H), 11.28 (1H, s, NH).

EXAMPLE 53

(3S)-3-(N-Benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine, 2,4 Hydrogen Oxalate.

a) 2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethyl alcohol

Prepared from 4-(1,2,4-triazol-1-ylmethyl)aniline (EP497512) as described for Intermediate 3, δ (250MHz, D_4-MeOH) 2.96 (2H, t, J=7.2Hz, CH_2), 3.80 (2H, t, J=7.2Hz, CH_2), 5.46 (2H, s, CH_2), 7.08 (1H, dd, J=1.7 and 8.6 Hz, Ar-H), 7.11 (1H, s, Ar-H), 7.33 (1H, d, J=8.6Hz, Ar-H), 7.58-7.59 (1H, d, J=1.7Hz, Ar-H), 7.97 (1H, s, Ar-H), 8.44 (1H, s, Ar-H).

b) (3S)-3-(N-Benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine, 2,4 Hydrogen Oxalate.

Prepared from 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyl alcohol and (3S)-N(H)-3-N-(benzyl)aminomethyl pyrrolidine as described for Example 41, mp 154-156°C, (Found: C, 56.92; H, 5.49; N, 13.40. $C_{25}H_{30}N_6 \cdot 2.4(C_2H_2O_4)$ requires C, 56.76; H, 5.56; N, 13.33%), m/e 415 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.72-1.86 (1H, m, CH of CH_2), 2.15-2.28 (1H, m, CH of CH_2), 2.70-2.84 (1H, m, CH), 3.00-3.62 (10H, m, 5 of CH_2), 4.16 (2H, s, CH_2), 5.44 (2H, s, CH_2), 7.07 (1H, d, J=8.6Hz, Ar-H), 7.27 (1H, s, Ar-H), 7.35 (1H, d, J=8.6Hz, Ar-H), 7.40-7.54 (5H, m, Ar-H), 7.63 (1H, s, Ar-H), 7.95 (1H, s, Ar-H), 8.64 (1H, s, Ar-H), 11.07 (1H, s, NH).

Examples 54 and 55 were prepared from 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyl alcohol and the appropriate pyrrolidine using the standard procedures.

EXAMPLE 54

(3S)-3-(N-[S]-α-Methylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.35 Hydrogen Oxalate. 0.1 Diethyl etherate.

mp: 195-197°C, (Found: C, 56.99; H, 5.65; N, 13.16. $C_{28}H_{32}N_6 \cdot 2.35(C_2H_2O_4) \cdot 0.3(H_2O) \cdot 0.1$(diethyl ether) requires C, 57.21; H, 5.91; N, 12.87%), m/e 429 $(M+1)^+$.

EXAMPLE 55

(3S)-3-(N-[R]-α-(Hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.25 Hydrogen Oxalate.

mp: 102-105°C, (Found: C, 56.60; H, 5.79; N, 13.02. $C_{28}H_{32}N_6O \cdot 2.25(C_2H_2O_4)$ requires C, 56.61; H, 5.69; N, 12.99%), m/e 445 $(M+1)^+$.

EXAMPLE 56

(3S)-3-(N-Benzyl-N-methyl)aminomethyl-1-[2-(5-(imidazol-1-yl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.0 Hydrogen Oxalate. Hemihydrate.

a) 2-[5-(Imidazol-1-yl)-1H-indol-3-yl]ethyl alcohol

Prepared from 4-(imidazol-1-yl)aniline (EP497512) as described for Intermediate 3, δ (360MHz, D_6-DMSO) 2.87 (2H, t, J=7.2Hz, CH_2), 3.64-3.70 (1H, m, CH_2-OH), 4.61 (1H, t, J=5.3Hz, OH), 7.08 (1H, s, Ar-H), 7.25-7.27 (2H, m, Ar-H), 7.44 (1H, d, J=8.8Hz, Ar-H), 7.64 (1H, d, J=2.5Hz, Ar-H), 7.70 (1H, d, J=2.1Hz, Ar-H), 8.11 (1H, s, Ar-H), 11.00 (1H, s, NH), m/e 228 $(M+1)^+$.

b) (3S)-3-(N-Benzyl-N-methyl)aminomethyl-1-[2-(5-(imidazol-1-yl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.0 Hydrogen Oxalate, Hemihydrate.

To a solution of (3S)-N(H)-3-(N-methyl-N-benzyl)aminomethylpyrrolidine (0.21g, 1.02mmol) in anhydrous DMF (3ml) was added K_2CO_3 (0.114g, 0.83mmol) and, dropwise, a solution of the mesylate of the preceding alcohol (0.168g, 0.55mmol) in DMF (7ml). The mixture was heated at 50°C for 1h and then at 70°C for 2h. After cooling, the solvent was removed under vacuum and the residue partitioned between CH_2Cl_2 (3 x 25ml) and water (25ml). The combined organics were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (90:10:1) to give the desired product (0.134g, 59% from the alcohol). The 2.0 hydrogen oxalate hemihydrate salt was prepared, mp 92°C (dec.), (Found: C, 59.53; H, 6.12; N, 11.83. $C_{26}H_{31}N_5 \cdot 2(C_2H_2O_4) \cdot 0.5\ H_2O$ requires C, 59.79; H, 6.02; N, 11.62%), m/e 414 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.60-1.74 (1H, m, CH of CH_2), 2.09-2.20 (1H, m, CH of CH_2), 2.24 (3H, s, CH_3), 2.54-3.58 (11H, m, 5 of CH_2 and CH), 3.66 (2H, ABq, J=13.3Hz, CH_2), 7.16 (1H, s, Ar-H), 7.26-7.39 (7H, m, Ar-H), 7.51 (1H, d, J=8.5Hz, Ar-H), 7.73 (1H, d, J=1.2Hz, Ar-H), 7.85 (1H, d, J=2.0Hz, Ar-H), 8.26 (1H, s, Ar-H), 11.24 (1H, s, NH).

EXAMPLE 57

(3S)-3-(N-Benzyl-N-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.5 Hydrogen Oxalate.

Prepared from 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyl alcohol and (3S)-N(H)-3-(N-methyl-N-benzyl)aminomethylpyrrolidine using the procedure described for Example 41. The 2.0 hydrogen oxalate hemihydrate salt was prepared, mp 154-155°C, (Found: C, 57.10; H, 5.95; N, 12.66. $C_{26}H_{32}N_6 \cdot 2.5(C_2H_2O_4)$ requires C, 56.96; H, 5.70; N, 12.85%), m/e 429 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.60-1.72 (1H, m, CH of CH_2), 2.08-

2.20 (1H, m, CH of CH_2), 2.26 (3H, s, CH_3), 2.52-3.60 (11H, m, 5 of CH_2 and CH), 3.69 (2H, ABq, J=13.4Hz, CH_2), 5.42 (2H, s, CH_2), 7.05 (1H, d, J=8.5Hz, Ar-H), 7.25-7.35 (7H, m Ar-H), 7.60 (1H, s, Ar-H), 7.92 (1H, s, Ar-H), 8.58 (1H, s, Ar-H), 11.02 (1H, s NH).

EXAMPLE 58

(3R)-3-(N-Methyl-N-[S]-α-methylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.0 Hydrogen Oxalate. 0.17 Diethyl etherate.

a) (3R)-N(H)-3-(N-Methyl-N-[S]-α-methylbenzyl)aminomethylpyrrolidine

Glacial acetic acid (0.9ml, 15.7mmol) and sodium cyanoborohydride (0.495g, 7.88mmol) were added successively to a stirred solution of (3S)-N-*tert*-butyloxycarbonyl-3-(N-[S]-α-methylbenzyl)aminomethylpyrrolidine (1.92g, 6.31mmol) in methanol (150ml), at 0°C. A solution of formaldehyde (0.623g of a 38% w/v solution, 7.88mmol), in methanol (50ml), was added dropwise over 0.1h. The mixture was stirred at 0°C for 4.5h and then at +25°C for 1.25h before adding saturated K_2CO_3 solution (25ml) and removing the solvent under vacuum. Ethyl acetate (100ml) was added to the residue and washed with water (x1), saturated K_2CO_3 solution (x1) and brine (x1), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH (95:5) to give (3R)-N-*tert*-butyloxycarbonyl-3-(N-[S]-α-methylbenzyl-N-methyl)aminomethylpyrrolidine (2.02g, 100%).

A solution of the preceding carbamate (2.01g, 6.32mmol) in 90% HCO_2H (40ml) was stirred at 0°C for 2.75h and then at +25°C for 16h. The reaction was quenched by the addition of methanol and the solvents removed under vacuum. The residue was azeotroped with ethanol and then taken up into a small volume of water and basified with saturated K_2CO_3 solution. The aqueous was extracted with *n*-butanol (2 x 50ml), the

combined extracts evaporated *in vacuo* and the inorganics removed by trituration with CH_2Cl_2 and filtering. The filtrate was dried ($MgSO_4$) and evaporated and the residue chromatographed on silica gel, eluting with CH_2Cl_2/MeOH/NH_3 (15:8:1) to give the title pyrrolidine (1.25g, 89%), δ (250MHz, $CDCl_3$) 1.34 (3H, d, J=6.8Hz, CH_3), 1.52-1.67 (1H, m, CH of CH_2), 1.96-2.10 (1H, m, CH of CH_2), 2.17 (3H, s, CH_3), 2.25-2.52 (3H, m, CH of CH_2), 2.72 (1H, dd, J=11.3 and 7.3Hz, CH of CH_2), 3.10 (2H, dd, J=8.0 and 6.6Hz, CH of CH_2), 3.25 (1H; dd, J=11.3 and 7.3Hz, CH of CH_2), 3.57 (1H, q, J=6.8Hz, CH), 5.97 (1H, br s, NH), 7.20-7.34 (5H, m, Ar-H).

b) (3R)-3-(N-Methyl-N-[S]-α-methylbenzyl)aminomethyl-1-[2-5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.0 Hydrogen Oxalate. 0.17 Diethyl etherate.

The *title compound* was prepared from the preceding pyrrolidine and the mesylate of 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyl alcohol using the standard coupling procedure. The 2.0 hydrogen oxalate 0.17 diethyl etherate salt was prepared, mp 148-149°C, (Found: C, 59.82; H, 6.58; N, 13.32. $C_{27}H_{34}N_6 \cdot 2.0(C_2H_2O_4) \cdot 0.17$(diethyl ether) requires C, 59.90; H, 6.30; N, 13.23%), m/e 443 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.34 (3H, d, J=6.9Hz, CH_3), 1.60-1.71 (1H, m, CH of CH_2), 2.06-2.16 (1H, m, CH of CH_2), 2.17 (3H, s, CH_3), 2.40-2.66 (3H, m, CH of CH_2), 2.92-3.09 (3H, m, CH_2 and CH of CH_2), 3.29-3.50 (5H, m, 2 of CH_2 and CH of CH_2), 3.73 (1H, q, J=6.9Hz, CH), 5.45 (2H, s, CH_2), 7.09 (1H, d, J=8.4Hz, Ar-H), 7.22-7.38 (7H, m, Ar-H), 7.59 (1H, s, Ar-H), 7.91 (1H, s, Ar-H), 8.51 (1H, s, Ar-H), 10.87 (1H, s, NH).

EXAMPLE 59

(3R)-3-(N-Methyl-N-[R]-α-hydroxymethylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 1.9 Hydrogen Oxalate. Hemihydrate. 0.05 Diethyl etherate.

The *title compound* was prepared from (3R)-N(H)-3-(N-methyl-N-[R]-α-hydroxymethylbenzyl)aminomethylpyrrolidine and the mesylate of 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl alcohol using the general procedure. The 1.9 hydrogen oxalate hemihydrate 0.05 diethyl etherate salt was prepared, mp 154-155°C, (Found: C, 57.26; H, 6.26; N, 12.75. $C_{27}H_{34}N_6O \cdot 1.9(C_2H_2O_4) \cdot 0.5\ H_2O \cdot 0.05$(diethyl ether) requires C, 57.25; H, 6.09; N, 12.92%), m/e 459 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.63-1.72 (1H, m, CH of CH_2), 2.04-2.14 (1H, m, CH of CH_2), 2.19 (3H, s, CH_3), 2.51-2.68 (3H, m, CH and CH_2), 3.00-3.10 (3H, m, CH of CH_2 and CH_2), 3.30-3.50 (5H, 2 of CH_2 and CH of CH_2), 3.63-3.89 (3H, m, CH and CH_2), 5.43 (2H, s, CH_2), 7.07 (1H, d, J=8.3Hz, Ar-H), 7.24-7.36 (7H, m, Ar-H), 7.58 (1H, s, Ar-H), 7.89 (1H, s, Ar-H), 8.50 (1H, s, Ar-H), 10.86 (1H, s, NH).

EXAMPLE 60

(3R)-3-(N-Methyl -N-[S]-α-methylcyclohexylmethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine, 2.25 Hydrogen Oxalate, 0.17 Diethyl etherate.

Prepared from 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl alcohol and (3R)-N(H)-3-(N-methyl-N-[S]-α-methylcyclohexylmethyl) aminomethylpyrrolidine using previously described procedures. The 2.25 hydrogen oxalate 0.17 diethyl etherate salt was prepared, mp 191-192°C, Found: C, 58.13; H, 7.40; N, 12.80. $C_{27}H_{40}N_6 \cdot 2.25(C_2H_2O_4) \cdot 0.17$(diethyl ether) requires C, 58.22; H, 7.02; N, 12.66%), m/e 449 $(M+1)^+$, δ (360MHz, D_6-DMSO) 0.82-0.93 (2H, m, CH_2), 0.91 (3H, d, J=6.6Hz, CH_3), 1.09-2.40 (4H, m, 2 of CH_2), 1.56-1.74 (5H, m, 2 of CH_2 and CH of CH_2), 1.88-1.96 (1H, m, CH), 2.06-2.16 (1H, m, CH of CH_2), 2.21 (3H, s, CH_3), 2.36-2.44 (1H, m, CH), 2.48-2.62 (3H, m, CH_2 and CH of CH_2), 3.00-3.10 (3H, m, CH_2 and CH of CH_2), 3.28-3.48 (5H, m, 2 of CH_2 and CH), 5.43 (2H, s, CH_2), 7.07 (1H, dd, J=1.6 and 8.4Hz, Ar-H), 7.24 (1H, d, J=1.6Hz, Ar-H),

7.35 (1H, d, J=8.4Hz, Ar-H), 7.58 (1H, s, Ar-H), 7.89 (1H, s, Ar-H), 8.49 (1H, s, Ar-H), 10.85 (1H, s, NH).

EXAMPLE 61

(3R)-3-(3-[R]-Hydroxy-2-[R]-phenylpiperidin-1-yl)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.35 Hydrogen Oxalate.

a) (3R)-N(H)-3-(3-[R]-Hydroxy-2-[R]-phenylpiperidin-1-yl) methylpyrrolidine

A mixture of (3R)-N-*tert*-butyloxycarbonyl-3-(methylsulphonyloxymethyl)pyrrolidine (1.0g, 3.58mmol) and N(H)-3-[R]-hydroxy-2-[R]-phenylpiperidine (3.17g, 17.92mmol), in toluene (12ml), was heated in a sealed tube at 150°C for 8h. The solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (2 x 150ml) and water (30ml). The extracts were dried (Na_2SO_4) and evaporated and the residue chromatographed on silica gel eluting with CH_2Cl_2/MeOH (95:5) to give the desired 3-(piperidinylmethyl)pyrrolidine (1.09g, 85%). To this material was added formic acid (20ml) and the solution stirred at +25°C for 16h. The formic acid was removed under reduced pressure and the residue basified with saturated K_2CO_3 solution. The aqueous was extracted with CH_2Cl_2 (8 x 100ml), the combined extracts dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_3 (30:8:1) to give the title-pyrrolidine (0.79g, 100%).

b) (3R)-3-(3-[R]-Hydroxy-2-[R]-phenylpiperidin-1-yl)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 2.35 Hydrogen Oxalate.

Prepared from the preceding pyrrolidine and the mesylate of 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethyl alcohol using the standard

coupling procedure. The 2.35 hydrogen oxalate salt was prepared, mp 118°C, (Found: C, 58.24; H, 6.22; N, 11.82. $C_{29}H_{36}N_6O \cdot 2.35(C_2H_2O_4)$ requires C, 58.14; H, 5.89; N, 12.07%), m/e 485 $(M+1)^+$, δ (360MHz, D_6-DMSO) 1.52-3.72 (21H, m, 3 of CH and 9 of CH_2), 5.42 (2H, s, CH_2), 7.06 (1H, dd, J=1.5 and 8.6Hz, Ar-H), 7.21 (1H, d, J=1.5Hz, Ar-H), 7.25-7.43 (6H, m, Ar-H), 7.57 (1H, s, Ar-H), 7.93 (1H, s, Ar-H), 8.58 (1H, s, Ar-H), 11.03 (1H, s, NH).

EXAMPLE 62

(3R)-3-(3-[R]-Hydroxy-2-[R]-phenylpiperidin-1-yl)methyl-1-[2-(5-(1,2,4-triazol-1-yl)-1H-indol-3-yl)ethyl]pyrrolidine. Sesquioxalate.

Prepared from (3R)-N(H)-3-(3-[R]-hydroxy-2-[R]-phenylpiperidin-1-yl)methylpyrrolidine and 2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethyl alcohol using the general procedure. The sesquioxalate salt was prepared, mp 192-193°C, (Found: C, 64.49; H, 6.30; N, 13.83. $C_{28}H_{34}N_6O \cdot 1.5(C_2H_2O_4)$ requires C, 61.48; H, 6.16; N, 13.87%), m/e 471 $(M+1)^+$, δ (250MHz, D_6-DMSO) 1.40-3.60 (21H, 3 of CH and 9 of CH_2), 7.16-7.60 (8H, m, Ar-H), 7.99 (1H, s, Ar-H), 8.20 (1H, s, Ar-H), 9.17 (1H, s, Ar-H), 11.27 (1H, s, NH).

EXAMPLE 63

4-Hydroxy-4-(phenylsulfinyl)methyl-1-[3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl]piperidine. Hydrogen Oxalate.

To a stirred solution of methyl phenyl sulphoxide (0.1268g, 0.904mmol), in THF (2ml), cooled under nitrogen to -78°C, was added dropwise, over 5 minutes, a 1.0M solution of lithium *bis*(trimethylsilyl)amide in THF (0.90ml, 0.900mmol), keeping the temperature below -77°C. The mixture was then stirred at -78°C for 30 minutes before adding by cannula, over 10 minutes, a stirred mixture of

4-keto-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine (0.1324g, 0.409mmol) in THF (2ml), cooled under nitrogen to -78°C. The reaction mixture was stirred at < -70°C for 2.25h, then allowed to warm to +10°C over 10 minutes before quenching with saturated NH_4Cl solution (1ml). The mixture was then partitioned between ethyl acetate (25ml) and saturated K_2CO_3 solution (20ml). The aqueous layer was reextracted with more ethyl acetate (3 x 25ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 90:10:1), then alumina, 3-5% MeOH/CH_2Cl_2, then silica gel, CH_2Cl_2/MeOH/NH_3, 92:8:0.8) to give 30.9mg (16%) of the *title compound* free base as a colourless oil. The oxalate salt was prepared in methanol-diethyl ether; mp 124°C (softens). (Found: C, 57.53; H, 5.84, N, 11.92. $C_{28}H_{29}N_5O_2S \cdot (C_2H_2O_4) \cdot 0.18(C_4H_{10}O) \cdot 0.6\ H_2O$ requires: C, 57.62, H, 5.93; N, 12.12%). δ_H (360MHz, DMSO-d_6) 1.74 (1H, m), 1.90-2.08 (5H, m), 2.77 (2H, m), 2.90-3.18 (8H, m), 7.32-7.35 (2H, m), 7.51 (1H, d, J=8.6Hz), 7.55-7.62 (3H, m), 7.66-7.68 (2H, m), 7.81 (1H, s), 9.03 (2H, s), 11.18 (1H, s); m/e (ES) 464 (M^++1).

EXAMPLE 64

(3R)-3-(2-[R,S]-Phenylpiperidin-1-yl)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl)ethyl]pyrrolidine. 1.8 Hydrogen Oxalate. 0.75 Hydrate.

The *title compound* was prepared using the procedures described for Example 61. The 1.8 hydrogen oxalate 0.75 hydrate salt was prepared, mp 184-185°C, (Found: C, 60.78; H, 6.67; N, 12.77. $C_{29}H_{36}N_6 \cdot 1.8(C_2H_2O_4) \cdot 0.75\ H_2O$ requires C, 60.78; H, 6.43; N, 13.05%); m/e 469 $(M+1)^+$.

EXAMPLE 65

4-([3,3-Dimethylpiperidin-1-yl]methyl)-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine. Hydrogen Oxalate.

a) 6-Aza-6-benzyl-1-oxaspiro[2.5]octane

Dimethyl sulphoxide (50ml) was added dropwise to a stirred, cooled (10°C) mixture of sodium hydride (1.85g of a 55% oil dispersion, 0.0423mol) and trimethylsulphoxonium iodide (8.0g, 0.0423mol) under a nitrogen atmosphere. After addition the cooling bath was removed and the mixture stirred at room temperature for 30 minutes, then cooled to 7°C and treated with a solution of 1-benzyl-4-piperidone (8.0g, 0.0423mol) in dimethyl sulphoxide (50ml). After addition the reaction mixture was stirred at room temperature for 15 minutes then at 50°C for 1 hour. The mixture was then stirred whilst cooling to room temperature then quenched with water (20ml). After stirring for a further 10 minutes the mixture was poured into water (250ml) and extracted with toluene (3 x 100ml). The combined organics were washed with water (200ml), dried (sodium sulphate) then evaporated to give the *title compound* as a pale yellow oil (7.4g, 86%). MS, ES^+, m/z = 204 for $(M+H)^+$; δ (360MHz, D_6-DMSO) 1.41-1.48 (2H, m) and 1.63-1.71 (2H, m, piperidine 3-CH_2 and 5-CH_2), 2.43-2.51 (4H, m, piperidine 2-CH_2 and 6-CH_2), 2.58 (2H, s, CH_2O), 3.51 (2H, s, CH_2Ph), 7.18-7.38 (5H, m, Ar-H).

b) 1-Benzyl-4-(3,3-dimethylpiperidin-1-yl)methyl-4-hydroxy piperidine

A solution of 6-aza-6-benzyl-1-oxaspiro[2.5]octane (2.0g, 9.84mmol) and 3,3-dimethylpiperidine (6.7ml, 49.2mmol) in ethanol (20ml) was heated at reflux for 3 hours. The reaction mixture was evaporated and the residue partitioned between dichloromethane (20ml) and water (20ml). The organic layer was separated, washed with water (20ml) then extracted with 2M hydrochloric acid (2 x 20ml). The combined aqueous

was washed with Et_2O (20ml) then basified to pH=12 with 40% sodium hydroxide solution and extracted with dichloromethane (4 x 20ml). The combined organics were dried (potassium carbonate) then evaporated to give the *title compound* as a colourless oil (2.16g, 69%). MS, ES^+, m/z = 317 for $(M+H)^+$; δ (250MHz, D_6-DMSO) 0.90 (6H, s, 2 x CH_3), 1.09-1.14 (2H, m, CH_2), 1.34-1.62 (6H, 3 x CH_2), 2.13 (4H, s, 2 x CH_2N), 2.25-2.45 (6H, 3 x CH_2N), 3.43 (2H, s, CH_2Ph), 3.80 (1H, s, OH), 7.19-7.34 (5H, m, Ar-H).

c) 4-(3,3-Dimethylpiperidin-1-yl)methyl-4-hydroxypiperidine

The foregoing benzyl-piperidine (2.03g, 6.42mmol) in methanol (60ml) was treated with formic acid (90%, 1ml), ammonium formate (1.21g, 19.3mmol) then 10% palladium on carbon (500mg). The reaction mixture was stirred at room temperature for 18h, then filtered and evaporated. The residue was partitioned between dichloromethane (80ml), methanol (10ml) and 10% potassium carbonate solution (20ml). The organic layer was separated and the aqueous extracted with dichloromethane (2 x 50ml). The combined organic layers were dried (potassium carbonate), then evaporated to give a gum which was purified using a short silica column, eluting with dichloromethane/methanol/ ammonia (5:1:0.1) to give the *title compound* as a colourless oil which solidified on standing (1.0g, 69%), mp 48-52°C; MS, ES^+, m/z = 227 for $(M+H)^+$; δ (250MHz, D_6-DMSO) 0.90 (6H, s, 2 x CH_3), 1.10-1.14 (2H, m, CH_2), 1.24-1.54 (6H, m, 3 x CH_2), 2.11 (2H, s, CH_2N), 2.11-2.13 (2H, m, CH_2N), 2.34-2.39 (2H, m, CH_2N), 2.52-2.60 (2H, m, CH_2N), 2.69-2.79 (2H, m, CH_2N), 3.80 (1H, br s, OH).

d) 4-([3,3-Dimethylpiperidin-1-yl]methyl)-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine, Hydrogen Oxalate.

3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propan-1-ol (300mg, 1.23mmol) was converted to the mesylate as previously described. This

mesylate (343mg) in propan-2-ol (70ml) was treated with 4-(3,3-dimethylpiperidin-1-yl)methyl-4-hydroxypiperidine (315mg, 1.39mmol) and potassium carbonate (192mg, 1.39mmol) then heated at reflux, with stirring, for 20h. The reaction mixture was evaporated then the residue was partitioned between dichloromethane (40ml) and water (20ml). The organic layer was separated then the aqueous was re-extracted with dichloromethane (40ml). The combined organics were dried (potassium carbonate) then evaporated to give a yellow gum (512mg) which was purified by column chromatography on silica using dichloromethane/methanol/ammonia (9:1:0.1→5:1:0.1) to give the *title compound* free base as a colourless gum (130mg, 27%). The hydrogen oxalate salt had mp 125-132°C. δ (360MHz, D_6-DMSO) 0.94 (6H, s, 2 x CH_3), 1.19-1.27 (4H, m, 2 x CH_2), 1.55-1.59 (2H, m, CH_2), 1.64-1.70 (2H, m, CH_2), 1.80-1.92 (2H, m, CH_2), 2.04-2.09 (2H, m, $CH_2CH_2CH_2$), 2.38-2.62 (6H, m, 3 x CH_2N), 2.78 (2H, t, J=7Hz, CH_2-indole), 3.00-3.18 (4H, m, 2 x CH_2N), 3.34-3.40 (2H, m, CH_2N), 7.32-7.35 (2H, m, Ar-H), 7.51 (1H, d, J=8Hz, Ar-H), 7.82 (1H, d, J=2Hz, Ar-H), 9.03 (2H, s, triazole-H), 11.20 (1H, s, indole-NH). (Found: C, 54.43; H, 6.98; N, 11.25. $C_{26}H_{38}N_6O \cdot 2.8(C_2H_2O_4) \cdot 0.5(C_2H_5)_2O$ requires C, 54.55; H, 6.62; N, 11.36%). MS, ES^+, m/z = 451 for $(M+H)^+$.

EXAMPLE 66

4-Hydroxy-4-([1,2,3,4-tetrahydroisoquinolin-2-yl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine, Hydrogen Oxalate.

a) 1-Benzyl-4-hydroxy-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl piperidine

The *title compound* was obtained (2.3g, 82%) from 6-aza-6-benzyl-1-oxaspiro[2.5]octane and 1,2,3,4-tetrahydroisoquinoline, mp 57-58°C. MS, ES^+, m/z = 337 for $(M+H)^+$.

b) 4-Hydroxy-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl piperidine

The *title compound* was obtained (1.01g, 69%) from the foregoing benzyl-piperidine, formic acid, ammonium formate and 10% palladium on carbon in methanol, mp 92-93°C. MS, ES^+, m/z = 247 for $(M+H)^+$; δ (360MHz, D_6-DMSO) 1.36-1.52 (4H, m, 2 x CH_2), 2.39 (2H, s, CH_2N), 2.55-2.62 (2H, m, CH_2N), 2.72-2.78 (2H, m, CH_2N), 2.80 (4H, s, CH_2Ph and CH_2N), 3.69 (2H, s, NCH_2Ph), 3.98 (1H, s, OH), 7.00-7.12 (4H, m, Ar-H).

c) 4-Hydroxy-4-([1,2,3,4-tetrahydroisoquinolin-2-yl]methyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propylpiperidine. Hydrogen Oxalate.

The *title compound* free base (191mg, 38%) was obtained from 4-hydroxy-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl piperidine and the mesylate obtained from 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol. The hydrogen oxalate salt had mp 160-165°C. δ (360MHz, D_6-DMSO) 1.66-1.94 (4H, m, 2 x CH_2), 1.98-2.10 (2H, m, $CH_2CH_2CH_2$), 2.58 (2H, br s, CH_2N), 2.77 (2H, t, J=7Hz, CH_2-indole), 2.83-2.87 (2H, m), 2.91-2.95 (2H, m), 3.00-3.18 (4H, m) and 3.30-3.40 (2H, m, 4 x CH_2N, CH_2-Ph), 3.82 (2H, s, N- CH_2-Ph), 7.00-7.15 (4H, m, Ar-H), 7.30-7.35 (2H, m, Ar-H), 7.51 (1H, d, J=8Hz, Ar-H), 7.80 (1H, s, Ar-H), 9.02 (2H, s, triazole-H), 11.19 (1H, s, indole-NH). (Found: C, 57.82; H, 5.81; N, 11.96. $C_{28}H_{34}N_6O \cdot 2.35(C_2H_2O_4)$ requires C, 57.57; H, 5.72; N, 12.31%). MS, ES^+, m/z = 471 for $(M+H)^+$.

EXAMPLE 67

4-Hydroxy-4-([*N*-isobutyl-*N*-methyl]aminomethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine

a) 6-Aza-6-*t*-butyloxycarbonyl-1-oxaspiro[2.5]octane

Dimethyl sulphoxide (100ml) was added dropwise to a stirred, cooled (10°C) mixture of sodium hydride (3.70g of a 55% oil dispersion, 0.0846mol) and trimethylsulphoxonium iodide (18.6g, 0.0846mol) under a

nitrogen atmosphere. After addition the cooling bath was removed and the mixture stirred at room temperature for 30 minutes, then cooled to 5°C and was treated with a solution of *N*-*t*-butoxycarbonyl-4-piperidone (16.86g, 0.0846mol) in dimethylsulphoxide (50ml). The cooling bath was removed and the reaction mixture stirred at room temperature for 15 minutes, then at 50°C for 1 hour. The mixture was stirred whilst cooling to room temperature then quenched with water (40ml) and stirred for a further 10 minutes. The reaction mixture was poured into water (600ml) and extracted with toluene (4 x 300ml). The combined organics were washed with water (300ml), dried (sodium sulphate) then evaporated to give an oil which was eluted through a short silica column using ethyl acetate/n-hexane (1:1) to give a colourless solid (10.0g, 55%), mp 49-51°C; δ (360MHz, D_6-DMSO) 1.35-1.40 (2H, m, CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.60-1.67 (2H, m, CH_2), 2.65 (2H, s, CH_2O), 3.33-3.41 (2H, m, CH_2), 3.46-3.54 (2H, m, CH_2). (Found: C, 61.88; H, 9.05; N, 6.42. $C_{11}H_{19}NO_3$ requires C, 61.95; H, 8.98; N, 6.57%). MS, ES^+, m/z = 214 for $(M+H)^+$.

b) <u>1-*t*-Butyloxycarbonyl-4-hydroxy-4-([*N*-isobutyl-*N*-methyl]aminomethyl)piperidine</u>

A mixture of the preceding compound (3g, 0.014mol) and isobutylamine (7ml, 0.0704mol) was heated in ethanol (30ml) at 60°C for 2h. The reaction mixture was evaporated to dryness and the residue eluted through a short silica column using dichloromethane/methanol/ammonia (9:1:0.1) to give 1-*t*-butyloxycarbonyl-4-hydroxy-4-(*N*-isobutylaminomethyl)piperidine (3.4g, 85%) as a colourless viscous gum, MS, ES^+, m/z = 287 for $(M+H)^+$. This amine (3.3g, 0.0115mol) in methanol (30ml) was treated with formaldehyde (1.4ml of a 37% aqueous solution, 0.0173mol) and acetic acid (3.3ml, 0.0575mol). After 5 minutes the solution was treated portionwise with sodium cyanoborohydride (1.09g, 0.0173mol) and the mixture was stirred at room temperature for 2h then quenched with saturated aqueous potassium carbonate (50ml). The

methanol was evaporated and the aqueous extracted with dichloromethane (4 x 50ml). The combined organics were dried (potassium carbonate) then evaporated to give a yellow gum which was eluted through a short silica column using dichloromethane/methanol (10:1) to give the *title compound* as a colourless gum (2.63g, 76%). δ (360MHz, D_6-DMSO) 0.83 (6H, d, J=7Hz, 2 x CH_3), 1.35-1.48 (4H, m, 2 x CH_2) overlapped with 1.38 (9H, s, $C(CH_3)_3$), 1.61-1.69 (1H, m, CH), 2.11 (2H, d, J=7Hz, CH_2CH), 2.22 (3H, s, NCH_3), 2.23 (2H, s, CH_2N), 3.02-3.08 (2H, m, CH_2N), 3.60 (2H, d, J=13Hz, CH_2N), 4.09 (1H, s, OH); MS, ES^+, m/z = 301 for $(M+H)^+$.

c) 4-Hydroxy-4-([*N*-isobutyl-*N*-methyl]aminomethyl)piperidine

The foregoing amine (2.55g, 8.49mmol) in dichloromethane (30ml) was treated with trifluoroacetic acid (6.5ml, 84.9mmol) and the solution was left standing for 18h, then evaporated and partitioned between saturated aqueous potassium carbonate (15ml) and dichloromethane (40ml) containing methanol (2ml). The organic layer was separated and the aqueous re-extracted with dichloromethane (3 x 40ml). The combined organics were dried (potassium carbonate) then evaporated to give a pale yellow gum (1.7g) which was eluted through a short silica column using dichloromethane/methanol/ammonia (5:1:0.1) to give the *title compound* as a viscous colourless gum (1.44g, 85%). δ (360MHz, D_6-DMSO) 0.84 (6H, t, J=7Hz, 2 x CH_3), 1.31-1.47 (1H, m, CH), 2.11 (2H, d, J=7Hz, NCH_2CH), 2.21 (2H, s, CH_2N), 2.23 (3H, s, NCH_3), 2.57-2.63 (2H, m, CH_2N), 2.73-2.80 (2H, m, CH_2N); MS, ES^+, m/z = 201 for $(M+H)^+$.

d) 4-Hydroxy-4-([*N*-isobutyl-*N*-methyl]aminomethyl)-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine

The *title compound* (230mg, 65%) was obtained from 4-hydroxy-4-([*N*-isobutyl-*N*-methyl]aminomethyl)piperidine and the mesylate, obtained from 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol, in

propan-2-ol using potassium carbonate as base, mp>60°C. δ (360MHz, D_6-DMSO) 0.84 (6H, d, J=6.5Hz), 2 x CH_3), 1.37-1.49 (2H, m, CH_2), 1.49-1.60 (2H, m, CH_2), 1.60-1.72 (1H, m, CH), 1.75-1.86 (2H, m, $CH_2\underline{CH_2}CH_2$), 2.11 (2H, d, J=7Hz, $\underline{CH_2}CH$), 2.21 (2H, s, CH_2N), 2.22 (3H, s, NCH_3), 2.20-2.35 (4H, m) and 2.37-2.52 (2H, m, 3 x CH_2N), 2.71 (2H, t, J=7Hz, CH_2-indole), 3.77 (1H, s, OH), 7.26 (1H, d, J=2Hz, Ar-H), 7.28 (1H, dd, J_1=2Hz, J_2=8Hz, Ar-H), 7.47 (1H, d, J=8Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.00 (2H, s, triazole-H), 11.05 (1H, s, indole-NH); MS, ES^+, m/z = 425 for $(M+H)^+$. (Found: C, 66.38; H, 8.71; N, 18.90. $C_{24}H_{36}N_6O \cdot 0.65\ H_2O$ requires C, 66.07; H, 8.62; N, 19.26%).

EXAMPLE 68

4-*N*-Benzyl-*N*-(2-hydroxyethyl)aminomethyl]-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine.

a) 1-*t*-Butyloxycarbonyl-4-hydroxy-4-([2-hydroxyethyl]aminomethyl)piperidine

The *title compound* was prepared from 6-aza-6-*tert*-butyloxycarbonyl-1-oxaspiro[2.5]octane and ethanolamine. MS, ES^+, m/z = 275 for $(M+H)^+$.

b) 1-*t*-Butyloxycarbonyl-4-hydroxy-4-(*N*-benzyl-*N*-[2-hydroxyethyl] aminomethyl)piperidine

The *title compound* was prepared (0.59g, 62%) from the foregoing piperidine, benzaldehyde, sodium cyanoborohydride and acetic acid in methanol. MS, ES^+, m/z = 365 for $(M+H)^+$, δ (360MHz, D_6-DMSO) 1.30-1.45 (4H, m, 2 x CH_2), 1.39 (9H, s, 3 x CH_3), 2.48 (2H, s, CH_2N), 2.54 (2H, t, J=6Hz, CH_2N), 3.06 (2H, br s, 2 x CH), 3.44 (2H, q, J=6Hz, CH_2O), 3.57 (2H, d, J=13Hz, 2 x CH), 3.71 (2H, s, $NC\underline{H_2}Ph$), 4.32 (1H, s, OH), 4.47 (1H, t, J=6Hz, OH), 7.22-7.36 (5H, m, Ar-H).

c) 4-(*N*-Benzyl-*N*-[2-hydroxyethyl]aminomethyl)-4-hydroxypiperidine

The *title compound* was obtained (0.44g, 100%) from the foregoing piperidine and trifluoroacetic acid in dichloromethane. MS, ES^+, m/z = 265 for $(M+H)^+$, δ (360MHz, D_6-DMSO) 1.37-1.42 (4H, m, 2 x CH_2), 2.46 (2H, s, CH_2N), 2.54-2.62 (2H, m, 2 x CH), 2.53 (2H, t, J=6Hz, CH_2N), 2.73-2.81 (2H, m 2 x CH), 3.45 (2H, t, J=6Hz, CH_2O), 3.71 (2H, s, NCH_2Ph), 4.14 (1H, br s, OH), 4.50 (1H, s, OH), 7.20-7.38 (5H, m, Ar-H).

d) 4-[*N*-Benzyl-*N*-(2-hydroxyethyl)aminomethyl]-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine

The *title compound* (155mg, 30%) was obtained from 4-(4-[*N*-benzyl-*N*-(2-hydroxyethyl)]aminomethyl)-4-hydroxypiperidine and the mesylate prepared from 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol in propan-2-ol using potassium carbonate as base, mp 75-78°C. δ (360MHz, D_6-DMSO) 1.41-1.46 (4H, m, 2 x CH_2), 1.76-1.80 (2H, m, $CH_2CH_2CH_2$), 2.20-2.40 (6H, m, 3 x CH_2N), 2.44 (2H, s, CH_2N), 2.53 (2H, t, J=6Hz, CH_2N), 2.69 (2H, t, J=7Hz, CH_2-indole), 3.43 (2H, q, J=6Hz, CH_2O), 3.70 (2H, s, NCH_2Ph), 4.04 (1H, s, OH), 4.45 (1H, t, J=6Hz, OH), 7.19-7.35 (7H, m), 7.46 (1H, d, J=8Hz) and 7.77 (9H, d, J=2Hz, 9 x Ar-H), 9.01 (2H, s, triazole-H), 11.05 (1H, s, indole-NH); MS, ES^+, m/z = 489 for $(M+H)^+$. (Found: C, 68.41; H, 7.21; N, 16.29. $C_{28}H_{36}N_6O_2 \cdot 0.2(C_4H_{10}O)$ requires C, 68.71; H, 7.60; N, 16.69%).

EXAMPLE 69

4-[*N*-(2,2-Dimethylpropyl)-N-methylaminomethyl]-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine.

a) 4-[*N*-(2,2-Dimethylpropyl)aminomethyl]-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine

The *title compound* was obtained (240mg, 75%) from 4-aminomethyl-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine, sodium cyanoborohydride, trimethylacetaldehyde and acetic acid in methanol, mp>55°C. MS, ES^+, m/z = 425 for $(M+H)^+$; δ (360MHz, D_6-DMSO) 0.85 (9H, s, 3 x CH_3), 1.40-1.52 (4H, m, 2 x CH_2), 1.75-1.86 (2H, m, $CH_2CH_2CH_2$), 2.27 (2H, s, CH_2N), 2.20-2.35 (4H, m, 2 x CH_2N), 2.39-2.50 (2H, m, CH_2N), 2.42 (2H, s, CH_2N), 2.71 (2H, t, J=7Hz, CH_2-indole), 4.00 (1H, s, OH), 7.26 (1H, d, J=2Hz, Ar-H), 7.29 (1H, dd, J_1=2Hz, J_2=8Hz, Ar-H), 7.47 (1H, d, J=8Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.00 (2H, s, triazole-H), 11.05 (1H, s, indole-NH).

b) 4-[*N*-(2,2-Dimethylpropyl)-*N*-methylaminomethyl]-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine.

The *title compound* was obtained (100mg, 74%) from the foregoing amine and formaldehyde in the presence of acetic acid and sodium cyanoborohydride in methanol as solvent, mp>70°C. MS, ES^+, m/z = 439 for $(M+H)^+$; δ (360MHz, D_6-DMSO) 0.86 (9H, s, 3 x CH_3), 1.46-1.52 (4H, m, 2 x CH_2), 1.76-1.86 (2H, m, $CH_2CH_2CH_2$), 2.18 (2H, s, CH_2N), 2.20-2.38 (6H, m, 3 x CH_2N), 2.37 (3H, s, NCH_3), 2.42-2.52 (2H, m, CH_2N), 2.72 (2H, t, J=7Hz, indole-CH_2), 3.82 (1H, s, OH), 7.27 (1H, d, J=2Hz, Ar-H), 7.30 (1H, dd, J_1=2Hz, J_2=8Hz, Ar-H), 7.47 (1H, d, J=8Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.06 (1H, s, indole-NH). (Found: C, 67.40; H, 8.89; N, 18.62. $C_{25}H_{38}N_6O \cdot 0.5\ H_2O$ requires C, 67.08; H, 8.78; N, 18.77%).

EXAMPLE 70

4-([*N*-(R)-α-Hydroxymethylbenzyl-*N*-methyl]aminomethyl)-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine.

a) 1-*t*-Butyloxycarbonyl-4-hydroxy-4-([*N*-(R)-α-hydroxymethylbenzyl]aminomethyl)piperidine

The *title compound* was obtained (2g, 78%) from 6-aza-6-*tert*-butyloxycarbonyl-1-oxaspiro[2.5]octane and (R)-phenylglycinol.

b) 4-Hydroxy-4([*N*-(R)-α-hydroxymethylbenzyl]aminomethyl)piperidine

The foregoing protected piperidine (1.9g, 5.4mmol) was stirred with trifluoroacetic acid (5ml) in dichloromethane (10ml) for 3h. The solvent was evaporated and the residue azeotroped with toluene, then partitioned between water and dichloromethane and basified with saturated aqueous potassium carbonate. The organic layer was separated and the aqueous re-extracted with dichloromethane (x3). The combined organics were dried (sodium sulphate) then evaporated to give the product as a gum (600mg, 44%), δ (360MHz, D_6-DMSO) 1.32-1.52 (4H, m, 2 x CH_2), 2.56 (2H, s, CH_2N), 2.47-2.52 (2H, m, CH_2N), 2.70-2.76 (2H, m, CH_2N), 3.28 (1H, dd, J_1=J_2=9Hz, NCHPh), 3.42-3.47 (1H, m) and 3.59-3.63 (1H, m, CH_2OH), 4.12 (1H, br s, OH), 4.94 (1H, br s, OH), 7.20-7.35 (5H, m, Ar-H).

c) 4-([*N*-(R)-α-Hydroxymethylbenzyl]aminomethyl)-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine

The *title compound* was prepared (290mg, 68%) from the foregoing piperidine and the mesylate prepared from 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol in propan-2-ol using potassium carbonate as base, mp>55°C. MS, ES$^+$, m/z = 475 for (M+H)$^+$. (Found: C, 66.73; H, 7.30; N, 16.87. $C_{27}H_{34}N_6O_2 \cdot 0.8\ H_2O$ requires C, 66.32; H, 7.34; N, 17.19%.

d) 4-([*N*-(R)-α-Hydroxymethylbenzyl-*N*-methyl]aminomethyl)-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine.

The *title compound* was obtained (140mg, 90%) from the foregoing benzylamine, formaldehyde, sodium cyanoborohydride and acetic acid in methanol, mp>75°C. MS, ES$^+$, m/z = 489 for (M+H)$^+$; δ (360MHz,

D_6-DMSO) 1.40-1.56 (4H, m, 2 x CH_2), 1.72-1.88 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.23 (3H, s, NCH_3), 2.18-2.56 (6H, m, 3 x CH_2N), 2.36 (2H, s, CH_2N), 2.72 (2H, t, J=7Hz, indole-CH_2), 3.58-3.70 (2H, m, CHO and CH-phenyl), 3.80-3.88 (1H, m, CHO), 4.07 (1H, s, OH), 4.58 (1H, t, J=6Hz, OH), 7.20-7.33 (7H, m, Ar-H), 7.48 (1H, d, J=8Hz, Ar-H), 7.78 (1H, d, J=2Hz, Ar-H), 9.02 (2H, s, triazole-H), 11.07 (1H, s, indole-NH). (Found: C, 67.02; H, 7.60; N, 15.89. $C_{28}H_{36}N_8O_2 \cdot 0.4\ H_2O \cdot 0.6(C_2H_6O)$ requires C, 67.00; H, 7.78; N, 16.05%).

EXAMPLE 71

4-Hydroxy-4-([2-Pyridylmethyl]amino)methyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine.

The *title compound* was obtained using a procedure similar to 4-(benzylamino)methyl-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine, using 2-pyridinecarboxaldehyde in the final step. mp>55°C; δ (360MHz, D_6-DMSO) 1.40-1.53 (4H, m, 2 x CH_2), 1.72-1.87 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.20-2.37 (6H, m, 3 x CH_2N), 2.44 (2H, s, $C\underline{H}_2NH$), 2.71 (2H, t, J=7Hz, CH_2-indole), 3.80 (2H, s, $NHC\underline{H}_2$ pyridyl), 4.08 (1H, br s, OH), 7.20-7.32 (3H, m, Ar-H), 7.41 (1H, d, J=7Hz, Ar-H), 7.46 (1H, d, J=8Hz, Ar-H), 7.72 (1H, dd, J_1=2Hz, J_2=8Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 8.46 (1H, d, J=8Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.05 (1H, s, indole-NH). MS, ES$^+$, m/z = 446 for $(M+H)^+$. (Found: C, 62.07; H, 7.19; N, 19.57. $C_{25}H_{31}N_7O \cdot 1.1\ H_2O \cdot 0.3(CH_2Cl_2)$ requires C, 61.91; H, 6.94; N, 19.97%).

EXAMPLE 72

4-Hydroxy-4-([2-methylphenylmethyl]amino)methyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine, Hydrogen Oxalate.

The *title compound* was obtained using a procedure similar to 4-(benzylamino)methyl-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine. The hydrogen oxalate salt had mp>138°C (dec); δ (360MHz, D_6-DMSO) 1.70-1.90 (4H, m, 2 x CH_2), 2.00-2.10 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.34 (3H, s, CH_3), 2.70-2.80 (2H, m, CH_2-indole), 2.89 (2H, s, $C\underline{H}_2NH$), 3.00-3.10 (4H, m) and 3.20-3.30 (2H, m, 3 x CH_2N), 4.06 (2H, s, $NHC\underline{H}_2Ar$), 7.16-7.26 (3H, m, Ar-H), 7.30-7.35 (2H, m, Ar-H), 7.43-7.52 (2H, m, Ar-H), 7.80 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.19 (1H, s, indole-NH). MS, ES^+, m/z = 459 for $(M+H)^+$. (Found: C, 55.89; H, 6.03; N, 11.50. $C_{27}H_{34}N_6O \cdot 2.7(C_2H_2O_4)$ requires C, 55.46; H, 5.66; N, 11.98%).

EXAMPLE 73

4-Hydroxy-4-([N-2-methylphenylmethyl-N-methyl]amino)methyl-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine. Hydrogen Oxalate.

The *title compound* was prepared (45mg, 64%) from the foregoing amine, using the procedure described for 4-([N-Benzyl-N-methyl]amino) methyl-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine. The hydrogen oxalate salt had mp>110°C (dec); δ (360MHz, D_6-DMSO) 1.55-1.70 (4H, m, 2 x CH_2), 1.98-2.10 (2H, m, $CH_2C\underline{H}_2CH_2$), 2.32 (6H, s, 2 x CH_3), 2.47 (2H, s, CH_2N), 2.75 (2H, t, J=7Hz, CH_2-indole), 2.96-3.10 (4H, m) and 3.20-3.30 (2H, m, 3 x CH_2N), 3.58 (2H, s, $NC\underline{H}_2Ar$), 7.05-7.20 (3H, m, Ar-H), 7.25-7.40 (3H, m, Ar-H), 7.50 (1H, d, J=8Hz, Ar-H), 7.80 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.19 (1H, s, indole-NH). MS, ES^+, m/z = for 473 $(M+H)^+$. (Found: C, 56.93; H, 6.42; N, 11.97. $C_{28}H_{36}N_6O \cdot 2(C_2H_2O_4)$ requires C, 56.55; H, 6.38; N, 12.36%).

EXAMPLE 74

3-(Benzylamino)methyl-3-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)pyrrolidine.

a) 1-Benzyl-3-(*t*-butyloxycarbonylamino)methyl-3-hydroxypyrrolidine

3-Aminomethyl-1-benzyl-3-hydroxypyrrolidine was prepared from 1-benzyl-3-pyrrolidinone using the procedure described in *Synth. Commun.*, 1994, 24 (10), 1483. This crude amine (9.4g, 45mmol) in dichloromethane (200ml) was treated with di-*t*-butyl dicarbonate (10g, 45mmol) and the reaction mixture was stirred at room temperature for 48h. The solvent was evaporated and the crude product was purified by column chromatography on silica using methanol/dichloromethane (1:20). The *title compound* was obtained as a gum (2.3g, 17%). MS, ES^+, m/z = 307 for $(M+H)^+$; δ (250MHz, D_6-DMSO) 1.37 (9H, s, 3 x CH_3), 1.52-1.62 (1H, m, CH), 1.76-1.87 (1H, m, CH), 2.27 (1H, d, J=10Hz, C<u>H</u>NH), 2.42-2.64 (3H, m, C<u>H</u>NH, CH_2N), 3.00-3.09 (2H, m, CH_2N), 3.52 (2H, s, C<u>H</u>$_2$Ph), 4.67 (1H, s, OH), 6.61 (1H, t, J=6Hz, NH), 7.18-7.33 (5H, m, Ar-H).

b) 3-(*t*-Butyloxycarbonylamino)methyl-3-hydroxypyrrolidine

A solution of the foregoing benzylamine (2.2g, 7.2mmol) in methanol (40ml) was treated with ammonium formate (1.1g) and 10% palladium on carbon (1.1g). The reaction mixture was stirred at room temperature for 4h, filtered, then evaporated. The residue was dissolved in water; basified with potassium carbonate then extracted with dichloromethane (x5). The combined organics were dried (sodium sulphate) then evaporated to give the required product as a gum (1.4g, 91%). δ (250MHz, D_6-DMSO) 1.38 (9H, s, 3 x CH_3), 1.48-1.69 (2H, m, CH_2), 2.52 (1H, d, J=11Hz, C<u>H</u>NH), 2.62 (1H, d, J=11Hz, C<u>H</u>NH), 2.65-

2.94 (2H, m, CH_2N), 3.06 (2H, d, J=6Hz, CH_2N), 4.59 (1H, br s, OH), 6.66 (1H, t, J=6Hz, NHCO).

c) 3-(*t*-Butyloxycarbonylamino)methyl-3-hydroxy-1-(3-[5-1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)pyrrolidine

The *title compound* was prepared (300mg, 30%) from the foregoing amine and the mesylate prepared from 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol in propan-2-ol using potassium carbonate as base, δ (250MHz, D_6-DMSO) 1.35 (9H, s, 3 x CH_3), 1.50-1.60 (1H, m, CH), 1.70-1.84 (3H, m, CH and $CH_2CH_2CH_2$), 2.26 (1H, d, J=10Hz, CHNH), 2.38 (2H, t, J=8Hz, CH_2N), 2.45-2.50 (2H, m, CH_2N), 2.58 (1H, d, J=10Hz, CHNH), 2.73 (2H, t, J=8Hz, CH_2-indole), 2.98-3.04 (2H, m, CH_2N), 4.64 (1H, s, OH), 6.60 (1H, t, J=6Hz, NHCO), 7.26-7.32 (2H, m, Ar-H), 7.46 (1H, d, J=8Hz, Ar-H), 7.78 (1H, d, J=2Hz, Ar-H), 9.02 (2H, s, triazole-H), 11.07 (1H, s, indole-NH).

d) 3-(Benzylamino)methyl-3-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)pyrrolidine

The *title compound* was prepared from the foregoing *t*-butyloxycarbonyl-protected compound as described for 4-(benzylamino)methyl-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine. mp>61°C. MS, ES^+, m/z = 431 for $(M+H)^+$; δ (360MHz, D_6-DMSO) 1.57-1.67 (1H, m, CH), 1.72-1.86 (3H, m, CH and $CH_2CH_2CH_2$)), 2.31-2.65 (8H, m 4 x CH_2N), 2.72 (2H, t, J=7Hz, CH_2-indole), 3.72 (2H, s, $NHCH_2Ph$), 4.55 (1H, s, OH), 7.15-7.32 (7H, m, Ar-H), 7.47 (1H, d, J=8Hz, Ar-H), 7.77 (1H, d, J=2Hz, Ar-H), 9.00 (2H, s, triazole-H), 11.06 (1H, s, indole-NH). (Found: C, 68.40; H, 6.53; N, 18.73. $C_{25}H_{30}N_6O \cdot 0.15(CH_2Cl_2)$ requires C, 68.14; H, 6.89; N, 18.96%).

EXAMPLE 75

3-(Benzylamino)methyl-3-hydroxy-1-(2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethyl)pyrrolidine.

The *title compound* was prepared from 3-(*t*-butyloxycarbonylamino) methyl-3-hydroxypyrrolidine and 1-chloro-2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethane (prepared from 2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethanol), followed by deprotection and functionalisation as described for 4-(benzylamino)methyl-4-hydroxy-1-(3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl)piperidine. mp>56°C. MS, ES$^+$, m/z = 417 for $(M+H)^+$; δ (360MHz, D_6-DMSO) 1.60-1.68 (1H, m, CH), 1.80-1.88 (1H, m, CH), 2.40-2.76 (8H, m, 4 x CH_2N), 2.84 (2H, t, J=7Hz, CH_2-indole), 3.72 (2H, s, $NHCH_2Ar$), 4.56 (1H, s, OH), 7.17-7.36 (7H, m, Ar-H), 7.47 (1H, d, J=8Hz, Ar-H), 7.78 (1H, d, J=2Hz, Ar-H), 9.01 (2H, s, triazole-H), 11.07 (1H, s, indole-NH). (Found: C, 67.40; H, 6.68; N, 19.54. $C_{24}H_{28}N_6O \cdot 0.5\ H_2O$ requires C, 67.74; H, 6.87; N, 19.75%).

EXAMPLE 76

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{(R)-α-[(carbamoyl) oxymethyl]benzylamino}piperidine. 1.75 Hydrogen Oxalate.

1. (R)-α-[(carbamoyl)oxymethyl]benzylamine

To a stirred solution of N-*tert*-butyloxycarbonyl-(R)-2-phenylglycinol (500mg, 2.1mmol) in anhydrous dichloromethane (10ml) was added dropwise, under nitrogen, trichloroacetyl isocyanate (275μl, 2.31mmol) over 2 minutes. The resulting clear colourless solution was stirred at room temperature for 45 minutes before neutral alumina (activity III; 12g) was added and stirring was continued for a further 40 minutes. The mixture was filtered, and the alumina was washed with dichloromethane (1 x 25ml) and with dichloromethane-ethyl acetate (1:1,

3 x 25ml). The filtrate was concentrated under vacuum to leave a white solid which was dissolved in dichloromethane-trifluoroacetic acid (3:1, 40ml) and the solution was allowed to stand at room temperature for 35 minutes. Solvents were removed under vacuum and the residue was azeotroped with methanol (2 x 50ml). Flash chromatography of the residue (silica gel, dichloromethane/methanol/ammonia, 90:10:1) gave 333mg (88%) of the *title compound* as a white solid: δ_H (360MHz, $CDCl_3$) 4.06 (1H, dd, J=11.8Hz and 9.5Hz), 4.21-4.28 (2H, m), 4.68 (2H, br s), 7.24-7.40 (5H, m); m/e (ES) 181 (M^++1).

2. 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{(R)-α-[(carbamoyl) oxymethyl]benzylamino}piperidine, 1.75 Hydrogen Oxalate.

The *title compound* was prepared in 65% yield from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and (R)-α-[(carbamoyl) oxymethyl]benzylamine using a similar method to that described for Example 8 (step 5), mp 135-140°C (EtOH). (Found: C, 56.56; H, 5.89; N, 15.34. $C_{27}H_{33}N_7O_2 \cdot 1.75(C_2H_2O_4)$ requires: C, 56.78; H, 5.70; N, 15.20%). δ_H (360MHz, DMSO-d_6; 353°K) 1.44-1.62 (2H, m), 1.74-1.82 (1H, m), 1.88-2.06 (3H, m), 2.55-2.68 (1H, m), 2.72-2.90 (4H, m), 2.91-3.00 (2H, m), 3.18-3.32 (2H, m), 3.92-4.06 (3H, m), 6.18 (2H, s,), 7.20-7.40 (7H, m), 7.48 (1H, d, J=8.6Hz), 7.73 (1H, d, J=2.0Hz), 8.87 (2H, s,), 10.97 (1H, s); m/e (ES) 488 (M^++1).

EXAMPLE 77

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(1R,2S)-2-hydroxy-1-phenyl]propylamino}piperidine, 2.45 Hydrogen Oxalate.

The *title compound* was prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and (1R,2S)-1-amino-1-phenyl-2-propanol (*Helv. Chim. Acta*, 1983, 66, 2274) using a similar method to that described for Example 8 (step 5), mp 130-135°C (EtOH-diethyl

ether). (Found: C, 56.47; H, 5.82; N, 12.37. $C_{27}H_{34}N_6O \cdot 2.45(C_2H_2O_4)$ requires: C, 56.41; H, 5.77; N, 12.37%). δ_H (360MHz, DMSO-d_6) 1.85 (3H, d, J=6.1Hz), 1.68-1.84 (2H, m), 1.90-2.16 (4H, m), 2.60-2.96 (7H, m), 3.28-3.42 (2H, m), 4.10-4.22 (2H, m), 7.26-7.42 (5H, m), 7.44-7.54 (3H, m), 7.78 (1H, d, J=1.9Hz), 9.01 (2H, s), 11.17 (1H, s); m/e (ES) 459 (M^++1).

EXAMPLE 78

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(1R,2R)-2-hydroxy-1-phenyl]propylamino}piperidine, 2.45 Hydrogen Oxalate.

The *title compound* was prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and (1R,2R)-1-amino-1-phenyl-2-propanol (*Helv. Chim. Acta*, 1983, 66, 2274) using a similar method to that described for Example 8 (step 5), mp 124-129°C (EtOH-diethyl ether). (Found: C, 56.40; H, 5.60; N, 12.50. $C_{27}H_{34}N_6O \cdot 2.45(C_2H_2O_4)$ requires: C, 56.41; H, 5.77; N, 12.37%). δ_H (360MHz, DMSO-d_6) 1.64-2.12 (6H, m), 2.60-2.78 (5H, m,), 2.80-2.92 (2H, m), 3.24-3.28 (2H, m), 3.87 (2H, br s), 7.26-7.50 (8H, m), 7.77 (1H, d, J=2.0Hz), 9.01 (2H, s), 11.16 (1H, s,); m/e (ES) 459 (M^++1).

EXAMPLE 79

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R,S)-1-hydroxy-2-phenylpropan-2-yl]amino}piperidine, 2.0 Hydrogen Oxalate.

To a stirred solution of 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine (0.133g, 0.41mmol) and (R,S)-2-amino-2-phenyl-1-propanol (76mg, 0.50mmol) in anhydrous methanol (8ml), under nitrogen, was added glacial acetic acid (94µl, 1.64mmol). After a further 30 minutes, sodium cyanoborohydride (32mg, 0.50mmol) was added and stirring was continued at room temperature for 2 days. Saturated aqueous potassium carbonate was added and the mixture was extracted

with ethyl acetate (4 x 25ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, dichloromethane/methanol/ammonia, 92:8:0.8) and the resulting oxazolidine was dissolved in ethanol (8ml) and glacial acetic acid (0.33ml, 5.76mmol) and sodium borohydride (0.58g, 15.2mmol) was added portionwise over 4 days whilst stirring at 20-80°C. The reaction mixture was then partitioned between water (75ml) and ethyl acetate (50ml). The aqueous layer was extracted with more ethyl acetate (3 x 30ml) and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Flash chromatography of the residue (silica gel, dichloromethane/ methanol/ammonia, 90:10:1 to 85:15:1.5) gave 12mg (7%) of the *title compound free base*. The oxalate salt was prepared in methanol-diethyl ether, mp 123-126°C. (Found: C, 56.47; H, 6.14; N, 12.53. $C_{27}H_{34}N_6O \cdot 2(C_2H_2O_4) \cdot 1.2\ H_2O \cdot 0.1(C_4H_{10}O)$ requires: C, 56.48; H, 6.25; N, 12.59%). δ_H (360MHz, DMSO-d_6) 1.56 (3H, s), 1.62-1.82 (4H, m), 1.95 (2H, m), 2.59-2.92 (7H, m), 3.25 (2H, m), 3.63 (2H, dd), 7.30-7.32 (3H, m), 7.38 (2H, t, J=7.5Hz), 7.49 (1H, d, J=8.6Hz), 7.55 (2H, d, J=7.4Hz), 7.77 (1H, d,), 9.01 (2H, s,), 11.16 (1H, s,); m/e (ES) 459 (M^+ +1).

EXAMPLE 80

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[[(R)-2-hydroxy-1-(4-fluorophenyl)ethyl]amino]piperidine, 2.0 Hydrogen Oxalate.

1. (R)-2-Amino-2-(4-fluorophenyl)ethanol

To a stirred 1.0M solution of lithium aluminium hydride in THF (23.5ml, 23.5mmol), cooled to 0°C under Ar, was added portionwise over 1h 45min solid (-)-4-fluoro-D-α-phenylglycine (1.98g, 11.7mmol). The reaction mixture was then stirred at room temperature overnight before carefully adding water (0.89ml), then 4N NaOH solution (0.89ml) and then water (2.68ml). The mixture was stirred for a few minutes, then

filtered, and the filtrate was evaporated *in vacuo*. Flash chromatography of the residue (silica gel, dichloromethane/methanol/ammonia, 90:10:1) gave 1.499g (82%) of the title compound as a white solid: δ_H (250MHz, $CDCl_3$) 3.52 (1H, dd, J=10.7 and 8.2Hz), 3.71 (1H, dd, J=10.7 and 4.4Hz), 4.06 (1H, dd, J=8.1 and 4.4Hz), 6.99-7.08 (2H, m), 7.28-7.34 (2H, m).

2. 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R)-2-hydroxy-1-(4-fluorophenyl)ethyl]amino}piperidine, 2.0 Hydrogen Oxalate.

This was prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and (R)-2-amino-2-(4-fluorophenyl)ethanol using a similar method to that described in Example 8 (step 5); mp 137°C (softens). (Found: C, 54.92; H, 5.49; N, 12.51. $C_{28}H_{31}FN_6O \cdot 2.0(C_2H_2O_4) \cdot 0.7\ H_2O \cdot 0.15(CH_4O) \cdot 0.12(C_4H_{10}O)$ requires C, 55.00; H, 5.76; N, 12.56%). δ_H (360MHz, DMSO-d_6) 1.72 (2H, m), 1.90-2.05 (4H, m), 2.66-2.86 (5H, m), 2.94 (2H, m), 3.37 (2H, m), 3.61 (2H, m), 4.19 (1H, m), 7.23 (2H, t, J=8.8Hz), 7.32-7.34 (2H, m), 7.49-7.55 (3H, m), 7.80 (1H, d), 9.02 (2H, s), 11.18 (1H, s); m/e (ES) 463 (M^++1).

EXAMPLE 81

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(1R,2R)-2-hydroxyindan-1-yl]amino}piperidine, 2.0 Hydrogen Oxalate.

1. (1R,2R)-1-Amino-2-hydroxyindan

Racemic *trans*-1-amino-2-hydroxyindan was resolved into its individual enantiomers using a similar procedure to that described in the literature: *J. Med. Chem.*, 1992, 35, 1685. The chiral purity of the individual enantiomers was assessed by HPLC analysis using a CrownPack CR(+) column (5% methanol in aqueous perchloric acid, pH 1.8; 1ml/min; 40°C; 210nm); retention time for (1R,2R)-enantiomer, 3.8min, 98.2% e.e. (retention time for (1S,2S)-enantiomer, 4.4min).

2. 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(1R,2R)-2-hydroxyindan-1-yl]amino}piperidine. 2.0 Hydrogen Oxalate.

The *title compound* was prepared from the product of the previous step and 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine using a similar method to that described for Example 8 (step 5), mp 156-158°C (methanol-diethyl ether). (Found: C, 58.17; H, 5.69; N, 13.19. $C_{27}H_{32}N_6O \cdot 2.0\ (C_2H_2O_4)$ requires: C, 58.48; H, 5.70; N, 13.20%). δ_H (360MHz, DMSO-d_6) 1.78-2.00 (2H, m), 2.00-2.10 (2H, m), 2.10-2.20 (1H, m), 2.20-2.40 (1H, m), 2.70-2.90 (5H, m), 2.90-3.00 (2H, m), 3.20-3.35 (1H, m), 3.35-3.50 (3H, m), 4.35-4.50 (2H, m), 7.20-7.40 (5H, m), 7.40-7.55 (2H, m), 7.81 (1H, s), 9.03 (2H, s), 11.19 (1H, s); m/e (ES) 457 (M^++1).

Examples 82-84 were prepared from 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and commercially available amines using a similar method to that described for Example 8 (step 5).

EXAMPLE 82

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R,S)-indan-1-yl]amino}piperidine. 2.55 Hydrogen Oxalate.

The oxalate salt was prepared from ethanol-diethyl ether, mp 122-128°C. (Found: C, 57.47; H, 5.55; N, 12.40. $C_{27}H_{32}N_6 \cdot 2.55(C_2H_2O_4)$ requires: C, 57.53; H, 5.58; N, 12.54%). δ_H (360MHz, DMSO-d_6) 1.84-2.28 (7H, m), 2.38-2.50 (1H, m), 2.72-3.16 (8H, m), 3.30-3.52 (3H, m), 4.85 (1H, br t), 7.24-7.38 (5H, m), 7.50 (1H, d, J=8.6Hz), 7.58 (1H, d, J=7.5Hz), 7.82 (1H, s), 9.03 (2H, s), 11.20 (1H, s); m/e (ES) 441 (M^++1).

EXAMPLE 83

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R,S)-1-(4-fluorophenyl)ethyl]amino}piperidine. 2.0 Hydrogen Oxalate.

The oxalate salt was prepared in methanol-diethyl ether, mp 149°C (softens). (Found: C, 57.44; H, 5.89; N, 13.33. $C_{26}H_{31}FN_6 \cdot 2(C_2H_2O_4) \cdot 0.17(C_4H_{10}O)$ requires: C, 57.65; H, 5.79; N, 13.15%). δ_H (360MHz, DMSO-$_6$)1.44 (3H, d, J=6.3Hz), 1.72 (2H, m), 1.91-2.13 (4H, m), 2.58-2.90 (7H, m), 3.30 (2H, m), 4.34 (1H, m), 7.25 (2H, t, J=8.8Hz), 7.31-7.33 (2H, m), 7.50 (1H, d, J=8.6Hz), 7.56 (2H, m), 7.79 (1H, d), 9.02 (2H, s), 11.17 (1H, s). m/e (ES) 447 (M^+ +1).

EXAMPLE 84

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R)-1-phenylpropan-2-yl]amino}piperidine. 2.0 Hydrogen Oxalate.

The oxalate salt was prepared in methanol-diethyl ether; mp 145°C (softens). (Found: C, 59.42; H, 6.69; N, 13.11. $C_{27}H_{34}N_6 \cdot 2(C_2H_2O_4) \cdot 0.3\ H_2O \cdot 0.25(C_4H_{10}O)$ requires: C, 59.44; H, 6.41; N, 13.00%), δ_H (360MHz, DMSO-d_6) 1.07 (3H, d, J=6.6Hz), 1.72 (2H, m), 1.94 (2H, m), 2.06 (2H, m), 2.42 (1H, m), 2.55-2.77 (6H, m), 3.15-3.29 (4H, m), 3.44 (1H, m), 7.26-7.34 (7H, m), 7.50 (1H, d, J=8.6Hz), 7.80 (1H, d), 9.03 (2H, s), 11.16 (1H, s); m/e (ES) 443 (M^+ +1).

EXAMPLE 85

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N-[(thiophen-3-yl)methyl]-N-methylamino}piperidine. 2.5 Hydrogen Oxalate. Di-hydrate.

The *title compound* was prepared using a similar method to that described for Example 30 (step 4). The oxalate salt was prepared and recrystallised from methanol-diethyl ether, mp 135-137°C. (Found:

C, 50.57; H, 5.43; N, 12.77. $C_{24}H_{30}N_6S \cdot 2.25(C_2H_2O_4) \cdot 2\ H_2O$ requires: C, 50.85; H, 5.76; N, 12.48%). δ_H (360MHz, DMSO-d_6) 1.35-1.50 (2H, m), 1.64-1.72 (2H, m), 1.72-1.84 (4H, m), 2.09 (3H, s), 2.22-2.34 (3H, m), 2.68-2.72 (2H, m), 2.86-2.90 (2H, m), 3.53 (2H, s), 6.99-7.01 (1H, m), 7.24-7.30 (3H, m), 7.43-7.47 (2H, m), 7.77-7.78 (1H, m), 9.01 (2H, s), 11.05 (1H, s); m/e (ES) 435 (M^++1).

EXAMPLE 86

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N-[(furan-3-yl)methyl]-N-methylamino}piperidine. 1.5 Hydrogen Oxalate. 2.25 Hydrate.

The *title compound* free base was prepared in a similar manner to that described in Example 30 (step 4). The oxalate salt was prepared and crystallised from methanol-diethyl ether, mp 128-130°C. (Found: C, 55.00; H, 6.74; N, 13.53. $C_{24}H_{30}N_6O \cdot 1.5(C_2H_2O_4) \cdot 2.5\ H_2O \cdot 0.14(C_4H_{10}O)$ requires: C, 54.76; H, 6.49; N, 13.90%). δ_H (250MHz, DMSO-d_6) 1.70-1.80 (2H, m), 1.80-2.10 (4H, m), 1.24 (3H, s), 2.60-2.80 (4H, m), 2.85-2.90 (2H, m), 3.30-3.40 (3H, m), 3.62 (2H, s), 6.46 (1H, s), 7.29-7.34 (2H, m), 7.48-7.51 (1H, m), 7.63 (2H, s), 7.80 (1H, s), 9.02 (2H, s), 11.18 (1H, s).

EXAMPLE 87

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(furan-3-yl)methylamino]piperidine. 2.0 Hydrogen Oxalate. 1.5 Hydrate.

A mixture of the product from Example 9 (free base; 765mg), ammonium formate (349mg) and palladium on carbon (10% w/w; 300mg) in anhydrous methanol (10ml) was refluxed, under nitrogen, for 3h. After cooling, the solids were filtered off and the filtrate was concentrated under vacuum. The residue was partitioned between water and *n*-butanol, and the organic layer was concentrated to yield 544mg of 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-aminopiperidine as a white foam.

δ_H (360MHz, DMSO-d_6) 1.20-1.40 (2H, m), 1.70-2.04 (6H, m), 2.35-2.41 (2H, m), 2.68-2.74 (2H, m), 2.89-2.94 (3H, m), 7.27-7.32 (2H, m), 7.47 (1H, d), 7.77 (1H, d), 9.02 (2H, s), 11.12 (1H, s).

A solution of the preceding amine (150mg, 0.46mmol), 3-furaldehyde (47mg, 0.49mmol), acetic acid (160µl, 2.77mmol) and sodium cyanoborohydride (30mg, 0.49mmol) in methanol (20ml) was stirred at room temperature, under nitrogen, for 18h. Volatiles were removed under vacuum and the residue was partitioned between saturated aqueous potassium carbonate and ethyl acetate. The aqueous phase was extracted three times with ethyl acetate and the combined organic solutions were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/methanol/ ammonia, 95:5:0.5 to 90:10:1) gave 73mg of the dialkylated amine (see Example 88) and 43mg of the *title compound* free base, from which the oxalate salt was prepared, mp 150-152°C (methanol-diethyl ether). (Found: C, 53.13; H, 5.48; N, 13.54. $C_{28}H_{28}N_6O \cdot 2.0(C_2H_2O_4) \cdot 1.5\ H_2O$ requires: C, 53.02; H, 5.77; N, 13.74%). δ_H (360MHz, DMSO-d_6) 1.60-1.70 (2H, m), 1.90-2.00 (2H, m), 2.05-2.10 (2H, m), 2.40-2.50 (5H, m), 2.70-2.80 (4H, m), 2.95-3.05 (1H, m), 3.15-3.20 (2H, m), 3.91 (2H, s), 6.57 (1H, s), 7.26-7.29 (2H, m), 7.47-7.49 (1H, m), 7.63 (1H, s), 7.70-7.73 (2H, m), 8.88 (2H, s), 10.95 (1H, s); m/e (ES) 405 (M^+ +1).

EXAMPLE 88

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N,N-[di-furan-3-yl)methyl]amino}piperidine, Dihydrogen oxalate hydrate.

The *title compound* free base was isolated from the reaction described in Example 87. The oxalate salt was prepared and crystallised from methanol-diethyl ether, mp 119-121°C. (Found: C, 56.18; H, 5.69; N, 12.40. $C_{28}H_{32}N_6O_2 \cdot 2(C_2H_2O_4) \cdot H_2O$ requires: C, 56.30; H, 5.61; N, 12.31%). δ_H (360MHz, DMSO-d_6) 1.70-1.90 (4H, m), 2.02-2.10 (2H, m),

2.70-2.90 (5H, m), 2.95-3.05 (2H, m), 3.35-3.50 (2H, m), 3.49 (4H, s), 6.38 (2H, s), 7.27-7.30 (2H, m),7.47-7.53 (5H, m), 7.74-7.75 (1H, m), 8.88 (2H, s), 11.00 (1H, s); m/e (ES) 485 (M^+ +1).

EXAMPLE 89

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[N-(3,3-dimethylallyl)-N-methylamino]piperidine. 1.25 Hydrogen Oxalate. 1.5 Hydrate.

A solution of 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-(N-methylamino)piperidine (417mg, 1.23mmol), prenylbromide (149µl, 1.29mmol) and potassium carbonate (170mg, 1.29mmol) in dimethylformamide (10ml) was heated to 80°C for 16h. The reaction was partitioned between water and ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and purified by chromatography using CH_2Cl_2/MeOH/NH_4OH (90:10:1) as eluant, to give the *title compound* free base. The oxalate salt was prepared and crystallised from methanol-diethyl ether, mp 128-130°C. (Found: C, 58.64; H, 7.44; N, 14.99. $C_{24}H_{34}N_6 \cdot 1.25(C_2H_2O_4) \cdot 1.5\ H_2O$ requires: C, 58.28; H, 7.29; N, 15.39%). δ_H (360MHz, DMSO-d_6; *free base*) 1.30-1.50 (2H, m), 1.59 (3H, s), 1.60-1.67 (2H, m), 1.68 (3H, s), 1.78-1.84 (4H, m), 2.09 (2H, s), 2.24-2.31 (3H, m), 2.69-2.73 (2H, m), 2.86-2.89 (2H, m), 2.95-2.97 (2H, m), 5.10-5.14 (1H, m), 7.23 (1H, s), 7.25-7.28 (1H, m), 7.45-7.47 (1H, m), 7.75-7.76 (1H, m), 8.96 (2H, s), 11.02 (1H, s); m/e (ES) 407 (M^+ +1).

EXAMPLE 90

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(N-allyl-N-methylamino)piperidine. 2.25 Hydrogen oxalate.

The *title compound* was prepared in a similar manner to that described in Example 89, using allyl bromide as the alkylating agent. mp 124-126°C (methanol-diethyl ether). (Found: C, 54.97; H, 6.24;

N, 14.11. $C_{22}H_{30}N_6 \cdot 2.25(C_2H_2O_4)$ requires: C, 54.77; H, 5.98; N, 14.46%). δ_H (360MHz, DMSO-d_6; *free base*) 1.34-1.45 (2H, m), 1.62-1.65 (2H, m), 1.77-1.84 (4H, m), 2.11 (3H, s), 2.27-2.31 (3H, m), 2.69-2.73 (2H, m), 2.86-2.89 (2H, m), 3.02-3.03 (2H, m), 5.05-5.08 (1H, m), 5.12-5.17 (1H, m), 5.72-5.82 (1H, m), 7.26-7.31 (2H, m), 7.46-7.48 (1H, m), 7.78-7.79 (1H, m), 9.01 (2H, s), 11.06 (1H, s); m/e (ES) 379 (M^++1).

EXAMPLE 91

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(indan-1-yl)aminolmethyl}piperidine, Dihydrogen Oxalate, 0.5 Hydrate.

The *title compound* was prepared in a similar manner to that described in Example 22 (step c), except that 1-aminoindan was used instead of (R)-α-methylbenzylamine. The oxalate was prepared and crystallised from methanol-diethyl ether, mp 140-142°C. (Found: C, 59.57; H, 6.11; N, 13.06. $C_{28}H_{34}N_6 \cdot 2(C_2H_2O_4) \cdot 0.5\ H_2O$ requires: C, 59.71; H, 6.11; N, 13.06%). δ_H (360MHz, DMSO-d_6; *free base*) 1.26-1.33 (2H, m), 1.40-1.55 (1H, m), 1.75-1.79 (4H, m), 1.83-1.95 (4H, m), 2.35-2.42 (3H, m), 2.58-2.63 (2H, m), 2.75-2.84 (3H, m), 2.94-3.02 (3H, m), 4.20-4.24 (1H, m), 7.12-7.15 (2H, m), 7.18-7.22 (3H, m), 7.30-7.35 (1H, m), 7.45-7.48 (1H, m), 7.56 (1H, s), 8.50 (2H, s), 8.60 (1H, s); m/e (ES) 455 (M^++1).

EXAMPLE 92

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[N-[(R)-α-(hydroxymethyl)benzyl]-N-methylaminolmethyl}piperidine, 2.0 Hydrogen Oxalate, 0.5 Hydrate.

The *title compound* free base was prepared from the amine of Example 31 using a similar method to that described for Example 10. The oxalate salt was prepared and crystallised from methanol-diethyl ether, mp 115-117°C. (Found: C, 57.96; H, 6.25; N, 12.66.

$C_{28}H_{36}N_6O \cdot 2.0(C_2H_2O_4) \cdot 0.5\ H_2O$ requires: C, 58.08; H, 6.24; N, 12.70%). δ_H (360MHz, $CDCl_3$; free base) 1.19-1.28 (2H, m), 1.68-1.95 (7H, m), 2.08-2.14 (4H, m), 2.23-2.31 (1H, m), 2.38-2.44 (2H, m), 2.74-2.80 (2H, m), 2.91-2.95 (2H, m), 3.59-3.65 (1H, m), 3.71-3.77 (1H, m), 3.92-4.00 (1H, m), 7.12-7.17 (4H, m), 7.30-7.34 (3H, m), 7.45-7.48 (1H, m), 7.56-7.57 (1H, m), 8.32 (1H, s), 8.47 (2H, s); m/e (ES) 473 ($M^+ + 1$).

EXAMPLE 93

(3R)-3-(Benzylthio)methyl-1-{2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethyl}pyrrolidine. Hydrogen Oxalate.

1. (3R)-3-(Benzylthio)methyl-1-(*tert*-butoxycarbonyl)pyrrolidine

To a stirred mixture of (3R)-1-(*tert*-butoxycarbonyl)-3-[(methanesulfonyloxy)methyl]pyrrolidine (0.5071g, 1.82mmol) and anhydrous potassium carbonate (0.3764g, 2.72mmol) in DMF (13ml), under argon, was added benzyl mercaptan (0.428ml, 3.65mmol) and the mixture was stirred overnight at room temperature, then at 60°C for 4h. The mixture was then partitioned between water (50ml) and diethyl ether (30ml). The aqueous layer was separated and reextracted with more diethyl ether (2 x 30ml). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 20% EtOAc/pet. ether) to give 0.5186 (93%) of the *title compound* as a colourless oil. δ_H (360MHz, $CDCl_3$) 1.45 (9H, s), 1.56 (1H, m), 1.99 (1H, m), 2.32 (1H, m), 2.45 (2H, t, J=6.4Hz), 2.97 (1H, m), 3.26 (1H, m), 3.61 (2H, m), 3.72 (2H, s), 7.22-7.40 (5H, m). m/e (ES+) 330 $(M+Na)^+$, 308 $(M+H)^+$, 252 $(M-CMe_3+2H)^+$, 234, 213, 208 $(M-Boc+2H)^+$.

2. (3R)-3-[(Benzylthio)methyl]pyrrolidine

To a stirred solution of (3R)-3-(benzylthio)methyl-1-(*tert*-butoxycarbonyl)pyrrolidine (0.2320g, 0.755mmol) in dichloromethane (3ml), under argon, was added trifluoroacetic acid (1ml) and the mixture was stirred at room temperature for 65 minutes before quenching with anhydrous methanol (2ml) and evaporating *in vacuo*. More methanol (2ml) was added to the residue and removed *in vacuo*. The residual oil was then dissolved in dichloromethane (25ml) and washed with 2N NaOH solution (10ml). The aqueous layer was reextracted with more dichloromethane (15ml) and the combined dichloromethane extracts were washed with saturated NaCl solution (10ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 85:15:1.5) to give 0.1210g (77%) of the *title compound* as a colourless oil. δ_H (250MHz,$CDCl_3$) 1.41 (1H, m), 1.90-2.00 (1H, m), 2.24 (1H, m), 2.42-2.50 (2H, m), 2.57 (1H, dd, J=6.5 and 11.0Hz), 2.82-2.99 (2H, m), 3.07 (1H, dd, J=7.3 and 11.0Hz), 3.72 (2H, s), 7.20-7.36 (5H, m); m/e (ES) 208 (M^+ +1).

3. (3R)-3-(Benzylthio)methyl-1-{2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethyl}pyrrolidine. Hydrogen Oxalate.

To a stirred solution of 3-[2-(methanesulfonyloxy)ethyl]-5-(1,2,4-triazol-4-yl)-1H-indole (0.1147g, 0.374mmol) and sodium carbonate (59.6mg, 0.562mmol) in 2-propanol (8ml), under argon, was added a solution of (3R)-3[(benzylthio)methyl]pyrrolidine (0.1165g, 0.562mmol) in 2-propanol (5ml) and the mixture was heated at reflux for 2h. After cooling, the reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 92:8:0.8) to give 0.1017g (65%) of the *title compound* free base as a colourless oil. The oxalate salt was prepared in methanol-diethyl ether; mp 79-91°C. (Found: C, 61.57; H, 5.94; N, 13.40. $C_{24}H_{27}N_5S \cdot C_2H_2O_4 \cdot 0.25(C_4H_{10}O)$ requires: C, 61.64; H, 6.03; N, 13.31%).

δ_H (360MHz, DMSO-d_6) 1.63 (1H, m), 2.10 (1H, m), 2.53 (2H), 2.92 (1H, m), 3.05 (2H, m), 3.25 (4H, m), 3.38 (1H, m), 3.76 (2H, s), 7.25 (1H, m), 7.32-7.33 (5H, m), 7.37 (1H, dd, J=9.1 and 2.1Hz), 7.52 (1H, d, J=8.7Hz), 7.88 (1H, d, J=2.0Hz), 9.03 (2H, s,), 11.26 (1H, s), among other signals; m/e (ES$^+$) 418 $(M+H)^+$.

EXAMPLE 94

(±)-1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(1-benzylamino-2-hydroxyethyl)piperidine, 2.0 Hydrogen Oxalate, 2.0 Hydrate.

1. (±)-2-[1-(*tert*-Butyloxycarbonyl)piperidin-4-yl]glycine methyl ester.

The *title compound* was prepared from 1-(*tert*-butyloxycarbonyl)-4-ketopiperidine and (±)-N-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester using a similar procedure to that described by U. Schmidt *et al.* (*Synthesis*, 1992, 487; *Synthesis*, 1984, 53); δ_H (250MHz, $CDCl_3$) 1.19-1.78 (5H, m), 1.45 (9H, s), 2.60-2.74 (2H, m), 3.31 (1H, d, J=5.7Hz), 3.73 (3H, s), 4.08-4.18 (2H, m).

2. (±)-2-[1-(*tert*-Butyloxycarbonyl)piperidin-4-yl]glycinol.

To a cooled (-78°C) solution of the ester from above (1.7g, 6.24mmol) in anhydrous tetrahydrofuran (50ml) was added lithium aluminium hydride (1.0M in THF; 6.24ml). The mixture was stirred at -78°C for 3h and at room temperature for 18h before water was added to produce a granular precipitate, which was removed by filtration. Concentration of the filtrate followed by flash chromatography of the remaining residue (silica gel, dichloromethane/methanol/ ammonia, 90:10:1) afforded the *title compound* as a colourless oil: m/e (ES) 245 (M^+ +1).

3. (±)-1-(*tert*-Butyloxycarbonyl)-4-(1-benzylamino-2-hydroxyethyl)piperidine.

A solution of the preceding glycinol (730mg, 2.99mmol), benzaldehyde (317mg, 2.99mmol), acetic acid (2ml) and sodium cyanoborohydride (188mg, 2.99mmol) in methanol (20ml) was stirred at room temperature for 18h. Saturated potassium carbonate solution was added to pH>8 and the methanol was removed under vacuum. The residue was diluted with water (20ml) and products were extracted with ethyl acetate (50ml), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, dichloromethane/methanol/ ammonia, 90:10:1) of the residue afforded 417mg (42%) of the *title compound* as a yellow oil; δ_H (360MHz, DMSO-d_6) 1.00-1.10 (1H, m), 1.38 (9H, s), 1.50-1.64 (2H, m), 1.64-1.78 (1H, m), 2.50-2.70 (2H, m), 3.31-3.34 (1H, m), 3.40-3.50 (1H, m), 3.60-3.80 (2H, m), 3.90-4.00 (2H, m), 4.40-4.43 (1H, m), 7.20-7.34 (5H, m).

4. (±)-4-(1-Benzylamino-2-hydroxyethyl)piperidine

A solution of the product from step 3 (417mg, 1.25mmol) in a mixture of trifluoroacetic acid and dichloromethane (1:10; 10ml) was stirred for 16h. The reaction was quenched by addition of saturated aqueous potassium carbonate and extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/ methanol/ammonia, 90:9:1) gave the *title compound* as a colourless solid; δ_H (250MHz, DMSO-d_6) 1.20-1.46 (2H, m), 1.56-1.76 (2H, m), 1.78-1.90 (1H, m), 2.20-2.30 (1H, m), 2.60-2.76 (2H, m), 3.10-3.60 (4H, m), 3.65 (1H, d, J=13.5Hz), 3.79 (1H, d, J=13.5Hz), 7.16-7.38 (5H, m).

5. (±)-1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(1-benzylamino-2-hydroxyethyl)piperidine, 2.0 Hydrogen Oxalate, 2.0 Hydrate.

The *title compound* was prepared from 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol and (±)-4-(1-benzylamino-2-hydroxyethyl)piperidine

using a similar procedure to that described for Example 98 (step 3). The oxalate salt was prepared and crystallised from ethanol-diethyl ether; mp 125-127°C. (Found: C, 55.23; H, 6.37; N, 11.66. $C_{27}H_{34}N_6O$-2($C_2H_2O_4$)·2 H_2O-0.3($C_4H_{10}O$) requires: C, 55.49; H, 6.51; N, 12.06%). δ_H (360MHz, DMSO-d_6) 1.50-1.70 (2H, m), 1.80-1.90 (2H, m), 1.90-2.10 (3H, m), 2.70-2.95 (5H, m), 2.95-3.10 (2H, m), 3.40-3.50 (2H, m), 3.55-3.70 (1H, m), 3.70-3.74 (1H, m), 4.04-4.19 (2H, m), 7.32-7.40 (6H, m), 7.48-7.52 (3H, m), 7.82 (1H, m), 9.03 (2H, s), 11.22 (1H, s); m/e (ES) 460 (M^++1).

EXAMPLE 95

1-{3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(hydroxymethyl)benzylamino]piperidine. 1.9 Hydrogen Oxalate.

1. 1-{3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl}-4-hydroxypiperidine.

The *title compound* was prepared from 4-(1,2,4-triazol-1-yl)-phenylhydrazine (EP497,512) and 5-(4-hydroxypiperidin-1-yl)pentanal dimethyl acetal using a similar method to that described for Example 8 (step 3). δ_H (250MHz, DMSO-d_6) 1.28-1.46 (2H, m), 1.64-2.04 (6H, m), 2.30 (2H, t, J=6.8Hz), 2.72 (4H, br t), 3.35-3.50 (1H, m), 4.53 (1H, d, J=4.2Hz), 7.25 (1H, d, J=2.2Hz), 7.44-7.54 (2H, m), 7.92 (1H, d, J=1.7Hz), 8.18 (1H, s), 9.18 (1H, s), 11.06 (1H, s); m/e (ES) 326 (M^++1).

2. 1-{3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine.

The *title compound* was prepared from the product of the previous step following a similar procedure to that described in Example 8 (step 4): pale yellow solid, mp 158-161°C (ethyl acetate); δ_H (360MHz, $CDCl_3$) 1.96 (2H, qn, J=7.3Hz), 2.46 (4H, t, J=6.1Hz), 2.55 (2H, t, J=7.2Hz), 2.75 (4H, t, J=6.1Hz), 2.86 (2H, t, J=7.5Hz), 7.12 (1H, d, J=2.2Hz), 7.40-7.48 (2H, m), 7.88 (1H, s), 8.12 (1H, s), 8.20 (1H, br s), 8.53 (1H, s); m/e (ES) 324 (M^++1).

3. 1-{3-[5-(1,2,4-Triazol-1-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(hydroxymethyl)benzylamino]piperidine, 1.9 Hydrogen Oxalate.

The *title compound* was prepared from the product of the previous step and (R)-2-phenylglycinol using a similar method to that described for Example 8 (step 5), mp 155-160°C (ethanol). (Found: C, 58.11; H, 6.04; N, 13.44. $C_{26}H_{32}N_6O \cdot 1.9(C_2H_2O_4)$ requires: C, 58.14; H, 5.86; N, 13.65%). δ_H (360MHz, DMSO-d_6) 1.56-1.76 (2H, m), 1.84-2.12 (4H, m), 2.60-2.96 (7H, m), 3.24-3.38 (2H, m), 3.50-3.64 (2H, m), 4.04-4.16 (1H, m), 7.26-7.56 (8H, m), 7.92 (1H, s), 8.18 (1H, s), 9.16 (1H, s), 11.14 (1H, s); m/e (ES) 445 (M^++1).

EXAMPLE 96

1-{3-[5-(Imidazol-1-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(methyl)benzylamino]piperidine, 2.6 Hydrogen Oxalate.

1. 4-(Imidazol-1-yl)nitrobenzene.

To a stirred solution of imidazole (34.1g, 0.50mol) in DMF (300ml) under Ar, was added portionwise, over 23 minutes, 60% NaH in oil (20.02g, 0.50mol). The mixture was then stirred at room temperature for 18 minutes before adding dropwise, over 40 minutes, a solution of 1-fluoro-4-nitrobenzene (70.62g, 0.50mol) in DMF (60ml). The mixture was then stirred at room temperature overnight. Water (600ml) was then added and the solid was filtered off, washed with water, then stirred in boiling ethyl acetate (400ml), allowed to cool and filtered, washing the solid with more ethyl acetate (50ml), then petroleum ether (250ml). The filtrate, now containing more solid, was refiltered and washed with petroleum ether. The combined solids were dried in a vacuum dessicator overnight to give 90.14g (95%) of the *title compound* as a yellow solid. δ_H (360MHz, DMSO-d_6) 9 (1H, t, J=1.1Hz), 7.97-8.03 (3H, m), 8.38 (2H, d, J=9.2Hz), 8.52 (1H, t).

2. 4-(Imidazol-1-yl)aniline. Dihydrochloride.

A mixture of 4-(imidazol-1-yl)nitrobenzene (89.60g, 0.474mol) and 10% palladium on carbon (4.50g) in ethanol (1200ml) and 5N HCl (189ml) was hydrogenated in two batches at 40psi for 80 minutes. Water (450ml) was then added to dissolve the product and the catalyst was removed by filtration, washing with more water, and the combined filtrates were evaporated *in vacuo*, using finally a freeze drier, to give 105.4g (96%) of the *title compound* as a cream solid. δ_H (250MHz, D_2O) 7.22 (2H, d, J=8.8Hz), 7.35 (1H, t, J=2.1Hz), 7.44 (2H, d, J=9.0Hz), 7.59 (1H, t, J=1.8Hz), 8.89 (1H, t, J=1.5Hz).

3. 4-(Imidazol-1-yl)phenylhydrazine. Dihydrochloride.

To a cooled (-15°C) and stirred suspension of 4-(imidazol-1-yl)-dihydrochloride (20g, 86.16mmol) in concentrated hydrochloric acid (100ml) was added dropwise, over 1 hour, a solution of sodium nitrite (6.25g, 9.05mmol) in water (40ml). After a further 10 minutes of stirring at -12°C, the mixture was quickly filtered to remove a solid, and the filtrate was added portionwise to a cooled (-20°C) and stirred solution of tin (II) chloride dihydrate (100g) in concentrated hydrochloric acid (50ml) at such a rate as to maintain the internal temperature below -10°C (15 minutes). The mixture was allowed to warm to 5°C over 30 minutes, and the solid was collected and washed with diethyl ether (4 x 100ml). The above solid was suspended in water (200ml) and basified with 4N sodium hydroxide solution and extracted with ethyl acetate (5 x 500ml). The combined organic solutions were dried (Na_2SO_4) and filtered. The filtrate was vigorously stirred while hydrogen chloride was being bubbled through the solution until a deep red mixture was obtained. Stirring was continued for a further 20 minutes to give a cream solid which was collected by filtration and dried over phosphorous pentoxide-potassium hydroxide under high vacuum to leave 12.7g (60%) of the *title compound*:

δ_H (360MHz, DMSO-d_6) 7.20 (2H, d, J=9.0Hz), 7.73 (2H, d, J=9.0Hz), 7.91 (1H, t, J=1.5Hz), 8.23 (1H, t, J=1.7Hz), 9.71 (1H, t, J=1.3Hz).

4. 1-{3-[5-(Imidazol-1-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine

The *title compound* was prepared from 4-(imidazol-1-yl)-phenylhydrazine dihydrochloride and 5-(4-hydroxypiperidin-1-yl)-pentanal dimethyl acetal using a similar method to that described for Example 8 (steps 3 and 4); δ_H (250MHz, $CDCl_3$) 1.96 (2H, qn, d=7.5Hz), 2.46 (4H, t, J=6.1Hz), 2.56 (2H, t, J=7.4Hz), 2.76 (4H, t, J=6.1Hz), 2.84 (2H, t, J=7.5Hz), 7.13 (1H, d, J=2.2Hz), 7.18-7.23 (2H, m), 7.30 (1H, t, J=1.2Hz), 7.44 (1H, d, J=8.5Hz), 7.58 (1H, d, J=2.1Hz), 7.84 (1H, t, J=1.0Hz), 8.41 (1H, br s); m/e (ES) 323 (M^++1).

5. 1-{3-[5-(Imidazol-1-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(methyl)benzylaminol]piperidine. 2.6 Hydrogen Oxalate.

This was prepared from 1-{3-[5-(imidazol-1-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine (0.201g, 0.62mmol) and (R)-(+)-α-methylbenzylamine (95.3μl, 0.75mmol) using a similar method to that described in Example 8 (step 5) to give 0.237g (89%) of the *title compound*, free base. The oxalate salt was prepared in methanol-diethyl ether, mp 130°C (softens). (Found: C, 58.63; H, 5.98; N, 10.33. $C_{27}H_{33}N_5 \cdot 2.6(C_2H_2O_4) \cdot 0.17(C_4H_{10}O)$ requires: C, 58.67; H, 5.96; N, 10.39%). δ_H (360MHz, DMSO-d_6) 1.50 (3H, d, J=6.6Hz), 1.75-1.82 (2H, m), 1.92-2.06 (3H, m), 2.12-2.16 (1H, m), 2.73 (4H, m), 2.90 (3H, m), 3.38 (2H, m), 4.40 (1H, q), 7.13 (1H, s), 7.27-7.30 (2H, m), 7.37-7.47 (4H, m), 7.53 (2H, d, J=7.0Hz), 7.68 (1H, s), 7.70 (1H, d), 8.20 (1H, s), 11.09 (1H, s); m/e (ES) 428 (M^++1).

EXAMPLE 97

1-{3-[5-(Imidazol-1-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(hydroxymethyl)benzylamino]piperidine. 3.0 Hydrogen Oxalate.

The *title compound* was prepared from 1-{3-[5-(Imidazol-1-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine (0.127g, 0.40mmol) and (R)-2-phenylglycinol (65mg, 0.48mmol) using a similar method to that described for Example 8 (step 5) to give 0.108g (62%) of the *title compound*, free base. The oxalate salt was prepared in methanol-diethyl ether; mp 99-102°C. (Found: C, 53.21; H, 5.45; N, 9.28. $C_{27}H_{33}N_5O \cdot 3(C_2H_2O_4) \cdot 0.11(C_4H_{10}O) \cdot 1.8\ H_2O$ requires: C, 53.25; H, 5.84; N, 9.29%). δ_H (360MHz, DMSO-d_6) 1.80-2.17 (6H, m), 2.72-2.96 (7H, m), 3.42 (2H, m), 3.71 (2H, d, J=5.6Hz), 4.32 (1H, m), 7.19 (1H, s), 7.28-7.31 (2H, m), 7.40-7.48 (4H, m), 7.52 (2H, d, J=6.7Hz), 7.72 (2H, s), 8.31 (1H, s), 11.11 (1H, s); m/e (ES) 444 (M^++1).

EXAMPLE 98

1-{3-[5-(1,2,4-Triazol-1-yl)methyl-1H-indol-3-yl]propyl}-4-[(R)-α-(hydroxymethyl)benzylamino]piperidine. 2.0 Hydrogen Oxalate. 1.5 Hydrate.

1. 3-[5-(1,2,4-Triazol-1-yl)methyl-1H-indol-3-yl]propan-1-ol

A mixture of palladium acetate (0.78g), lithium chloride (1.47g), sodium carbonate (18.49g), triphenylphosphine (1.8g), 5-triethylsilyl-4-pentyn-1-ol triethylsilyl ether (16.3g) and 2-iodo-4-[(1,2,4-triazol-1-yl)methyl]aniline (10.0g) in degassed anhydrous dimethylformamide (400ml) was heated at 100°C for 10h. under nitrogen. After cooling, the reaction was filtered, concentrated, and the residue was partitioned between water and ethyl acetate. The organic phase was dried ($MgSO_4$), concentrated and the residue was treated with 5N hydrochloric acid/

methanol (1:3; 400ml) for 3h at room temperature. The methanol was removed under vacuum, the aqueous residue was basified with sodium carbonate solution and it was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (silica gel, dichloromethane/methanol, 95:5) followed by trituration with petroleum ether, gave the *title compound* (56%) as a beige solid. δ_H (360MHz, DMSO-d_6) 1.74-1.82 (2H, m), 2.66-2.70 (2H, m), 3.43-3.49 (2H, m), 4.41-4.44 (1H, m), 5.42 (2H, s), 7.01-7.04 (1H, m), 7.11-7.12 (1H, m), 7.28-7.30 (1H, m), 7.51 (1H, s), 7.93 (1H, s), 8.60 (1H, s), 10.79 (1H, s).

2. 4-[(R)-α-(Hydroxymethyl)benzyl]aminopiperidine.

To a stirred solution of N-*tert*-butyloxycarbonyl-4-piperidinone (2g, 10mmol), (R)-(-)-phenylglycinol (1.65g, 12mmol), and glacial acetic acid (2.29ml, 40mmol) in methanol (200ml) was added sodium cyanoborohydride (754mg, 12mmol). After being stirred at room temperature, under nitrogen, for 16h, the mixture was basified with 4N sodium hydroxide and the methanol was removed under vacuum. The residue was diluted with water (35ml) and the product extracted with diethyl ether (2 x 200ml), washed with brine (1 x 40ml), dried (Na_2SO_4) and concentrated. Flash chromatography (silica gel, dichloromethane/ methanol/ammonia, 95:5:0.5) of the residue gave 2.91g (90.9%) of 1-*tert*-butyloxycarbonyl-4-[(R)-α-(hydroxymethyl)benzyl]aminopiperidine.

A solution of the above BOC-protected piperidine (2.9g) in trifluoroacetic acid (40ml) and dichloromethane (50ml) was allowed to stand at room temperature for 16h. Solvents were removed under vacuum and the residue was azeotroped with toluene/ethanol (5:1, 150ml). The residue was dissolved in 4N sodium hydroxide, extracted with dichloromethane (3 x 150ml) and the combined organic solutions were washed with brine (1 x 50ml), then dried (Na_2SO_4) and concentrated. Crystallisation from ethyl acetate/hexane (1:10, 200ml) afforded the *title*

compound as white crystals (1.4g, 70.4%); δ_H (360MHz, DMSO-d_6) 0.96-1.12 (2H, m), 1.52 (1H, d, J=12.0Hz), 1.78-2.06 (2H, br s and d, J=12.6Hz), 2.17-2.32 (3H, m), 2.76-2.90 (2H, m), 3.26 (1H, t, J=8.5Hz), 3.40 (1H, dd, J=10.5 and 4.5Hz), 3.83 (1H, dd, J=8.5 and 4.5Hz), 4.82 (1H, br s), 7.27-7.37 (5H, m); m/z (ES) 221 (M^+ +1).

3. 1-[3-[5-(1,2,4-Triazol-1-yl)methyl-1H-indol-3-yl]propyl]-4-[(R)-α-(hydroxymethyl)benzylamino]piperidine. 2.0 Hydrogen Oxalate. 1.5 Hydrate.

A solution of the product from Step 1 (209mg, 81mmol) in THF (10ml) was cooled to -40°C under nitrogen. Triethylamine (146µl) was added followed by methanesulfonyl chloride (75µl) and the reaction allowed to attain room temperature. The reaction was filtered and solvent removed *in vacuo*. The residue was partitioned between water-dichloromethane and the organic phase dried ($MgSO_4$) and concentrated.

A solution of the mesylate in THF (20ml) with diisopropyl-ethylamine (310µl) and the amine from step 2 (231mg) was heated for 4h at 40°C and 6h at 60°C. Sodium iodide (150mg) was added and heating continued for 17h in a foil covered reaction vessel. Saturated sodium chloride was added, solvent removed *in vacuo* and the residue extracted into *n*-butanol. The organic phase was concentrated, and chromatographed using methanol/dichloromethane/ammonia (15:84:1) as eluant, to give the *title compound* free base. The oxalate salt was prepared and crystallised from ethanol-diethyl ether. (Found: C, 58.97; H, 6.24; N, 13.56. $C_{26}H_{31}N_5O_2 \cdot 2(C_2H_2O_4) \cdot 1.5\ H_2O$ requires: C, 59.21; H, 6.11; N, 13.54%.) δ_H (360MHz, DMSO-d_6) 1.60-1.75 (2H, m), 1.85-2.10 (4H, m), 2.60-2.80 (4H, m), 2.80-2.95 (2H, m), 3.20-3.30 (2H, m), 3.50-3.60 (2H, m), 4.05-4.15 (1H, m), 5.42 (2H, s), 7.02-7.05 (1H, m), 7.16 (1H, m), 7.29-7.39 (4H, m), 7.44-7.50 (3H, m), 7.93 (1H, s), 8.60 (1H, s), 10.90 (1H, s); m/e 459 (M^+ +1).

EXAMPLE 99

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(methoxymethyl)benzylamino]piperidine, Dihydrogen Oxalate, Hydrate.

The *title compound* was prepared in a similar manner to that described in Example 8 (step 5) using (R)-(-)-1-amino-1-phenyl-2-methoxyethane (A.I. Meyers *et al.*, *J. Org. Chem.*, 1978, **43**, 892); mp 138-140°C (methanol-diethyl ether). (Found: C, 56.65; H, 6.03; N, 12.86. $C_{27}H_{34}N_6O \cdot 2(C_2H_2O_4) \cdot 1.0\ H_2O$ requires: C, 56.70; H, 6.14; N, 12.80%.) δ_H (360MHz, DMSO-d_6) 1.60-1.80 (2H, m), 1.90-2.20 (4H, m), 2.65-2.90 (5H, m), 2.90-3.05 (2H, m), 3.27 (3H, m), 3.27-3.40 (2H, m), 3.50-3.56 (2H, m), 4.20-4.30 (1H, m), 7.31-7.33 (5H, m), 7.46-7.51 (3H, m), 7.79 (1H, m), 9.02 (2H, s), 11.19 (1H, s); m/e (ES) 459 (M^++1).

EXAMPLE 100

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{N-[(R)-α-(methoxymethyl)benzyl]-N-methylamino}piperidine, 2.0 Hydrogen Oxalate, 0.6 Hydrate.

The *title compound* was prepared from the product of Example 99 following a similar method to that described for Example 10, mp 119-121°C. (Found: C, 57.65; H, 6.33; N, 13.02. $C_{28}H_{36}N_6O \cdot 2.0(C_2H_2O_4) \cdot 0.6\ H_2O$ requires: C, 57.93; H, 6.26; N, 12.67%). δ_H (360MHz, $CDCl_3$; free base) 1.60-1.91 (10H, m), 2.25 (3H, s), 2.33-2.37 (2H, m), 2.45-2.48 (1H, m), 2.72-2.77 (2H, m), 2.90-2.93 (2H, m), 3.29 (3H, s), 3.59-3.63 (2H, m), 3.69-3.73 (2H, m), 3.84-3.87 (2H, m), 7.11-7.14 (2H, m), 7.23-7.31 (6H, m), 7.44-7.47 (1H, m), 7.53-7.54 (1H, m), 8.40 (1H, s), 8.45 (2H, s); m/e (ES) 473 (M^++1).

EXAMPLE 101

1-{3-[5-(Imidazol-1-yl)-1H-indol-3-yl]propyl}-4-[(R)-α-(methoxymethyl)benzylamino]piperidine. 2.0 Hydrogen Oxalate. 1.5 Hydrate.

The *title compound* was prepared from 1-{3-[5-(imidazol-1-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine and (R)-α-(methoxymethyl)benzylamine using a similar procedure to that described for Example 8 (step 5); mp 128-130°C. (Found: C, 57.72; H, 6.19; N, 10.35. $C_{28}H_{35}N_5O \cdot 2.0(C_2H_2O_4) \cdot 1.5\ H_2O$ requires: C, 57.82; H, 6.37; N, 10.54%). δ_H (250MHz, DMSO-d_6) 1.55-1.80 (2H, m), 1.80-2.20 (4H, m), 2.60-2.85 (6H, m), 2.85-3.00 (2H, m), 3.23 (3H, s), 3.20-3.40 (2H, m), 3.40-3.60 (2H, m), 7.10 (1H, s), 7.24-7.46 (8H, m), 7.65-7.68 (2H, m), 8.18 (1H, s), 11.07 (1H, s); m/e (ES) 458 (M^++1).

EXAMPLE 102

1-{3-[5-(1,2,4-Triazol-1-yl)methyl-1H-indol-3-yl]propyl}-4-{[(R)-1-(4-fluorophenyl)-2-methoxyethyl]amino}piperidine. 2.0 Hydrogen Oxalate Hydrate.

1. (R)-2-Amino-2-(4-fluorophenyl)-1-methoxy ethane. Hydrogen chloride.

A solution of (R)-2-amino-2-(4-fluorophenyl)ethanol (Example 80, step 1) (600mg, 3.9mmol) in anhydrous THF (5ml) was added dropwise to a stirred suspension of sodium hydride (0.46g of 35% wt suspension in oil, washed with anhydrous pentane) in anhydrous THF (5ml). The reaction was stirred for 2h, treated with iodomethane (237μl) and allowed to stand for 18h. The reaction was partitioned between diethyl-ether and saturated aqueous sodium chloride. The organic phase was dried ($MgSO_4$), concentrated, and redissolved in diethyl ether. The solution was treated with hydrogen chloride-diethyl ether (10ml) and concentrated to a

yellow solid. Recrystallisation from ethyl acetate gave colourless needles (551mg). δ_H (250MHz, DMSO-d_6) 3.32 (3H, s), 3.57-3.72 (2H, m), 4.48-4.53 (1H, m), 7.24-7.32 (2H, m), 7.56-7.61 (2H, m), 8.6 (3H, br s).

2. 1-*tert*-Butyloxycarbonyl-4-[(R)-1-(4-fluorophenyl)-2-methoxyethyl]aminopiperidine

The product from above (250mg) and N-*tert*-butyloxycarbonyl-4-ketopiperidine were reacted as described in Example 98 (step 2). The crude product was reacted as described below (step 3).

3. 4-[(R)-1-(4-Fluorophenyl)-2-methoxyethyl]aminopiperidine hydrogen chloride

To a solution of the product from above (0.67g) in methanol (5ml) was added 1N hydrogen chloride-diethyl ether (5ml). The reaction was concentrated and recrystallised from methanol-ethyl acetate to give a colourless solid (367mg). δ_H (250MHz, d_4-methanol) 2.08-2.44 (4H, m), 2.84-3.08 (2H, m), 3.43 (2H, br s), 3.47 (3H, s), 3.76-3.96 (2H, m), 7.15-7.22 (2H, m), 7.61-7.66 (2H, m).

4. 1-{3-[5-(1,2,4-Triazol-1-yl)methyl-1H-indol-3-yl]propyl}-4-{[(R)-1-(4-fluorophenyl)-2-methoxyethyl]amino}piperidine. 2.0 Hydrogen Oxalate Hydrate.

The product from above (367mg) was reacted as described in Example 98 with the mesylate described in Example 98 (step 3) to give the *title compound*. (Found: C, 55.68; H, 6.12; N, 11.92. $C_{28}H_{35}FN_6O \cdot 2(C_2H_2O_4) \cdot H_2O$ requires: C, 55.81; H, 6.00; N, 12.20%.) δ_H (360MHz, DMSO-d_6) 1.52-1.70 (2H, m), 1.80-1.90 (1H, m), 1.90-2.12 (3H, m), 2.56-2.74 (4H, m), 2.74-3.04 (4H, m), 3.24 (3H, s), 3.28-3.54 (3H, m), 4.20 (1H, br s), 5.43 (2H, s), 7.04-7.06 (1H, m), 7.17-7.22 (3H, m), 7.30-7.33 (1H, m), 7.47-7.51 (3H, m), 7.94 (1H, s), 8.60 (1H, s), 10.92 (1H, s); m/e (ES) 491 (M^++1).

EXAMPLE 103

1-{3-[5-(1,2,4-Triazol-1-yl)methyl-1H-indol-3-yl]propyl}-4-[N-(4-fluorobenzyl)-N-methylamino]piperidine. 2 Hydrogen Oxalate. Hydrate.

1. 1-*tert*-Butyloxycarbonyl-4-(4-fluorobenzyl)aminopiperidine

4-Fluorobenzylamine (2.5g) and N-*tert*-butoxycarbonyl-4-piperidone (4g) were reacted as described in Example 98 (step 2), to give the title product as a yellow oil which crystallised (6.2g). δ_H (250MHz, $CDCl_3$) 1.22-1.37 (2H, m), 1.43 (9H, s), 1.82-1.94 (2H, m), 2.60-2.72 (1H, m), 2.74-2.84 (2H, m), 3.80 (2H, s), 3.94-4.10 (2H, m), 6.97 (2H, m), 7.26-7.31 (2H, m).

2. 1-*tert*-Butyloxycarbonyl-4-[N-(4-fluorobenzyl)-N-methylamino]piperidine

The product from above (6.2g) was reacted using a similar procedure to that described in Example 10 to give the title product as a colourless oil (5.66g). δ_H (250MHz, $CDCl_3$) 1.46 (9H, s), 1.46-1.57 (2H, m), 1.71-1.81 (2H, m), 2.17 (3H, s), 2.50-2.74 (3H, m), 3.53 (3H, s), 4.06-4.26 (2H, m), 6.95-7.02 (2H, m), 7.24-7.30 (2H, m).

3. 4-[N-(4-fluorobenzyl)-N-methylamino]piperidine

The product from above (2.73g) was deprotected using a similar procedure to that described in Example 98 (step 2). The amine was obtained as a yellow oil (1.81g). δ_H (360MHz, $CDCl_3$) 1.48-1.59 (2H, m), 1.81-1.85 (2H, m), 2.18 (3H, s), 2.30-2.44 (2H, br s), 2.48-2.64 (3H, m), 3.16-3.20 (2H, m), 3.53 (2H, s), 6.96-7.00 (2H, m), 7.24-7.28 (2H, m).

4. 1-{3-[5-(1,2,4-Triazol-1-yl)methyl-1H-indol-3-yl]propyl}-4-[N-(4-fluorobenzyl)-N-methylamino]piperidine. 2.0 Hydrogen Oxalate Hydrate.

The *title compound* was prepared using a similar method to that described in Example 98 (step 3) using the product from above (642mg) and the mesylate from Example 98 (step 3). The oxalate salt was prepared and crystallised from methanol-diethyl ether; mp 180-181°C. (Found: C, 56.83; H, 5.79, N, 12.78. $C_{27}H_{33}N_6F \cdot 2(C_2H_2O_4) \cdot H_2O$ requires C, 56.53; H, 5.97; N, 12.76%). δ_H (360MHz, DMSO-d_6) 1.80-1.95 (2H, m), 1.95-2.08 (4H, m), 2.24 (3H, s), 2.68-2.78 (2H, m), 2.80-2.98 (3H, s), 3.00-3.10 (2H, m), 3.40-3.54 (2H, m), 3.77 (2H, s), 5.44 (2H, s), 7.05-7.07 (1H, m), 7.16-7.21 (3H, m), 7.32-7.34 (1H, m), 7.40-7.44 (2H, m), 7.54 (1H, s), 7.95 (1H, s), 8.6 (1H, s), 10.93 (1H, s); m/e (ES) 461 (M^+ +1).

EXAMPLE 104

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(2-phenylpiperidin-1-yl)piperidine. 2.5 Hydrogen Oxalate. 1.5 Hydrate.

1. 1-*tert*-Butyloxycarbonyl-4-[2-phenylpiperidin-1-yl]piperidine

N-*tert*-Butyloxycarbonyl-4-piperidone (5g), 2-phenylpiperidine (4.03g) and titanium isopropoxide (8.9ml) were stirred at room temperature under a nitrogen atmosphere for 3h. The resulting orange solution was diluted with methanol (40ml), treated with sodium cyanoborohydride (1.6g), and stirred for 20h. Water (50ml) was added to give a granular precipitate which was removed by filtration through celite. The filtrate was partitioned between water-ethyl acetate, the organic phase separated, dried ($MgSO_4$) and concentrated. The residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of citric acid. The aqueous phase was basified to pH10 using 4N sodium hydroxide, and extracted into ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated. The residue was chromatographed using ethyl acetate-petroleum ether (20:80 to 50:50) to afford a partially purified mixture, which was dissolved in ethyl acetate. The organic phase

was washed with a saturated aqueous solution of citric acid. The aqueous phase was separated, basified to pH10 using 4N sodium hydroxide and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated to give the product in 3% yield. δ_H (250MHz, $CDCl_3$) 1.16-1.79 (19H, m), 2.21-2.29 (2H, m), 2.41-2.50 (2H, m), 2.90-3.04 (1H, m), 3.36-3.44 (1H, m), 3.92-4.10 (2H, m), 7.16-7.40 (5H, m).

2. 4-(2-Phenylpiperidin-1-yl)piperidine

The product from above (245mg) was deprotected as described in Example 98 (step 2). The product was obtained as a yellow solid (170mg). δ_H (360MHz, $CDCl_3$) 1.29-1.83 (10H, m), 2.10-2.18 (1H, m), 2.25-2.45 (3H, m), 2.97-3.06 (3H, m), 3.39-3.42 (1H, m), 7.21-7.30 (5H, m).

3. 1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-(2-phenylpiperidin-1-yl)piperidine, 2.5 Hydrogen Oxalate, 1.5 Hydrate.

The *title compound* was prepared from 3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propan-1-ol and 4-(2-phenylpiperidin-1-yl)piperidine using a similar method to that described for Example 36 (step b). The oxalate salt was prepared and crystallised from methanol-diethyl ether; mp 126-128°C. (Found: C, 56.42; H, 6.17; N, 11.56. $C_{29}H_{36}N_6 \cdot 2.5(C_2H_2O_4) \cdot 1.5\ H_2O$ requires: C, 56.66; H, 6.15; N, 11.66%). δ_H (360MHz, DMSO-d_6, 353°K) 1.30-1.50 (1H, m), 1.52-2.06 (12H, m), 2.30-2.70 (4H, m), 2.71-2.75 (2H, m), 2.80-2.88 (2H, m), 3.00-3.14 (1H, m), 3.24-3.40 (2H, m), 3.60-3.70 (1H, m), 7.25-7.38 (7H, m), 7.47-7.50 (1H, m), 7.71-7.72 (1H, m), 8.86 (2H, m), 10.93 (1H, m); m/e (ES) 469 $(M+1)^+$.

EXAMPLE 105

1-{3-[5-(1,2,4-Triazol-4-yl)-1H-indol-3-yl]propyl}-4-{[(R)-1-(4-fluorophenyl)-2-methoxyethyl]amino}piperidine, Hydrogen Oxalate.

(R)-2-Amino-2-(4-fluorophenyl)-1-methoxy ethane (Example 102, step 1) (310mg) and 1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}-4-ketopiperidine (487mg) were reacted as described in Example 8 (step 5) to give the *title compound*. The oxalate salt was prepared and crystallised from methanol-diethyl ether. (Found: C, 54.75; H, 5.94; N, 12.47. $C_{27}H_{33}FN_6 \cdot 2(C_2H_2O_4) \cdot 1.2\ H_2O$ requires: C, 54.89; H, 5.86; N, 12.39%). δ_H (360MHz, DMSO-d_6) 1.56-1.70 (2H, m), 1.82-1.94 (1H, s), 1.94-2.20 (3H, m), 2.54-2.68 (1H, m), 1.68-1.90 (4H, m) 1.90-3.06 (2H, m), 3.25 (3H, s), 3.28-3.42 (2H, m), 3.42-3.56 (2H, m), 4.20-4.30 (1H, m), 7.17-7.22 (2H, m), 7.31-7.34 (2H, m), 7.48-7.51 (3H, m) 7.79-7.80 (1H, m), 9.01 (2H, s), 11.17 (1H, s).

EXAMPLE 106

(3R)-3-(Benzylsulfinyl)methyl-1-{2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethyl}pyrrolidine. Hydrogen Oxalate.

1. (3R)-3-(Benzylsulfinyl)methyl-1-(*tert*-butoxycarbonyl)pyrrolidine

To a stirred solution of (3R)-3-(benzylthio)methyl-1-(*tert*-butoxycarbonyl)pyrrolidine (0.2553g, 0.830mmol) in ethyl acetate (15ml), under argon, cooled in a bath at ca. -40°C, was added portionwise 57-86% 3-chloroperoxybenzoic acid (0.2094g). The mixture was then allowed to warm to 0°C over 1.5h, before pouring into 5% $NaHCO_3$ solution (15ml). The organic layer was separated and washed with more 5% $NaHCO_3$ solution (15ml), then saturated NaCl solution (10ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 3% MeOH/CH_2Cl_2) to give 0.2381g (89%) of the *title compound* as a colourless oil. δ_H (250MHz, $CDCl_3$) 1.44 (9H, s), 1.61 (1H, m), 2.15 (1H, m), 2.52 (1H, m), 2.66 (2H, m), 3.00 (1H, m), 3.29 (1H, m), 3.43 (1H, m), 3.63 (1H, m), 3.96 (1H, d, J=12.9Hz), 4.07 (1H, d, J=12.9Hz), 7.28-7.30 (2H, m), 7.35-7.39 (3H, m). m/e (ES+) 324 $(M+H)^+$.

2. (3R)-3-[(Benzylsulfinyl)methyl]pyrrolidine

Using a similar method to that described in Example 93, step 2, (3R)-3-(benzylsulfinyl)methyl-1-(*tert*-butoxycarbonyl)pyrrolidine (0.2376g, 0.735mmol) was reacted with trifluoroacetic acid (1ml) in dichloromethane (3ml) to give, after work up, 0.1543g (94%) of the *title compound* as a white solid, which was used without further purification. δ_H (250MHz, $CDCl_3$) 1.47 (1H, m), 2.09 (1H, m), 2.52-2.72 (4H, m), 2.94 (2H, m), 3.19 (1H, m), 3.96 (1H, d, J=12.9Hz), 4.06 (1H, dd, J=12.9 and 3.6Hz), 7.27-7.43 (5H, m).

3. (3R)-3-(Benzylsulfinyl)methyl-1-{2-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]ethyl}pyrrolidine, Hydrogen Oxalate.

Using a similar method to that described in Example 93, step 3, (3R)-3-[(benzylsulfinyl)methyl]pyrrolidine (0.1500g, 0.672mmol) was reacted with 3-[2-(methanesulfonyloxy)ethyl]-5-(1,2,4-triazol-4-yl)-1H-indole (0.1375g, 0.449mmol) and sodium carbonate (71.3mg, 0.673mmol) in 2-propanol (15ml) to give 93.8mg (48%) of the *title compound* free base as a colourless solid. The oxalate salt was prepared in methanol-diethyl ether: mp 100-108°C. (Found: C, 57.77; H, 5.90; N, 12.36. $C_{24}H_{27}N_5SO \cdot C_2H_2O_4 \cdot 0.18(C_4H_{10}O) \cdot H_2O$ requires: C, 57.83; H, 5.96; N, 12.62%). δ_H (360MHz, DMSO-d_6) 1.80 (1H, m), 2.06 (1H, m), 2.79-2.86 (2H, m), 2.94 (1H, m), 3.09 (3H, m), 3.38 (4H, m), 3.62 (1H, m), 4.01 (1H, dd, J=3.4 and 12.7Hz), 4.18 (1H, dd, J=6.1 and 12.8Hz), 7.32-7.40 (7H, m), 7.52 (1H, d, J=8.6Hz), 7.89 (1H, s), 9.03 (2H, s), 11.29 (1H, s). m/e (ES+) 434 $(M+H)^+$.

EXAMPLE 107

(3R)-3-[(4-Fluorobenzylthio)methyl]-1-{2-(5-[(1,2,4-triazol-1-yl)methyl]-1H-indol-3-yl)ethyl}pyrrolidine, Hydrogen Oxalate.

1. (3R)-1-(*tert*-Butoxycarbonyl)-3-[(4-fluorobenzylthio)methyl]pyrrolidine

Using a similar method to that described in Example 93, step 1, (3R)-1-(*tert*-butoxycarbonyl)-3-[(methanesulfonyloxy)methyl]pyrrolidine (1.5000g, 5.37mmol) was reacted with 4-fluorobenzyl mercaptan (1.5511g, 10.91mmol) and potassium carbonate (1.1132g, 8.05mmol) in DMF (30ml) at room temperature for 24h to give 1.7507g (100%) of the *title compound* as a colourless oil. δ_H (360MHz, $CDCl_3$) 1.45 (9H, s), 1.60 (1H, m), 2.00 (1H, m), 2.44 (2H, m), 2.97 (1H, m), 3.28 (1H, m), 3.46 (2H, m), 3.69 (2H, s), 7.00 (2H, t, J=8.6Hz), 7.25-7.29 (2H, m). m/e (ES+) 348 $(M+Na)^+$, 326 $M+H)^+$, 270 $(M-CMe_3+2H)^+$.

2. (3R)-3-[(4-Fluorobenzylthio)methyl]pyrrolidine

A solution of (3R)-1-(*tert*-butoxycarbonyl)-3-[(4-fluorobenzylthio)methyl]pyrrolidine (0.5422g, 1.67mmol) in 90% formic acid (5ml) was stirred at room temperature for 23h. The solvents were removed *in vacuo* and the residue was dissolved in dichloromethane (25ml) and washed with 2N NaOH solution (10ml). The aqueous layer was reextracted with more dichloromethane (25ml) and the combined organic extracts were washed with saturated NaCl solution (10ml), dried (Na_2SO_4) and evaporated *in vacuo* to leave 0.3903g of the *title compound* as an oil. δ_H (360MHz, $CDCl_3$) 1.42 (1H, m), 1.94 (1H, m), 2.24 (1H, m), 2.45 (2H, m), 2.59 (1H, m), 2.92 (2H, m), 3.08 (1H, m), 3.69 (2H, s), 7.00 (2H, t, J=8.6Hz), 7.25-7.29 (2H, m).

3. (3R)-3-[(4-Fluorobenzylthio)methyl]-1-{2-(5-[(1,2,4-triazol-1-yl)methyl)-1H-indol-3-yl)ethyl}pyrrolidine. Hydrogen Oxalate.

To a stirred solution of 3-(2-hydroxyethyl)-5[(1,2,4-triazol-1-yl)methyl]-1H-indole (0.1425g, 0.588mmol) and triethylamine (0.107ml, 0.768mmol) in THF (10ml), cooled under argon in a bath at -40°C, was added dropwise methanesulfonyl chloride (56.0µl, 0.709mmol). The

mixture was then stirred at room temperature for 1.5h before diluting with ethyl acetate (40ml) and washing with brine (20ml). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was immediately dissolved in anhydrous 2-propanol (10ml) to which was added anhydrous potassium carbonate (0.1626g, 1.176mmol) followed by a solution of (3R)-3-[(4-fluorobenzylthio)methyl]pyrrolidine (0.1978g, 0.878mmol) in anhydrous 2-propanol (8ml). The mixture was then heated at reflux for 4h. After cooling, the solvents were removed *in vacuo* and the residue was partitioned between dichloromethane (25ml) and water (15ml). The aqueous layer was separated and reextracted with more dichloromethane (2 x 25ml). The combined organic layers were washed with saturated NaCl solution (20ml), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 94:6:0.6), then by preparative t.l.c. (silica gel, CH_2Cl_2/MeOH/NH_3, 92:8:0.8) to give 0.147g (56%) of the *title compound*, free base. The oxalate salt was prepared in methanol-diethyl ether; mp 68-71°C. (Found: C, 61.02; H, 5.65; N, 13.70. $C_{25}H_{28}FN_5S \cdot 0.8(C_2H_2O_4)$ requires: C, 61.25; H, 5.72; N, 13.43%). δ_H (360MHz, DMSO-d_6) 1.60 (1H, m), 2.07 (1H, m), 2.81 (1H, m), 2.96 (2H, m), 3.13 (4H, m), 3.27 (1H, m), 3.76 (2H, s), 5.43 (2H, s), 7.05 (1H, d, J=9.7Hz), 7.15 (2H, t, J=8.9Hz), 7.23 (1H, s), 7.32-7.39 (3H, m), 7.58 (1H, s), 7.94 (1H, s), 8.81 (1H, s), 10.97 (1H, s) among other signals. m/e (ES+) 450 $(M+H)^+$.

EXAMPLE 108

(3R)-3-[(4-Fluorobenzylsulfinyl)methyl)-1-{2-(5[(1,2,4-triazol-1-yl)methyl]-1H-indol-3-yl)ethyl}pyrrolidine, Hydrogen Oxalate.

1. (3R)-1-(*tert*-Butoxycarbonyl)-3-[(4-fluorobenzylsulfinyl)methyl]pyrrolidine

Using a similar procedure to that described in Example 107, step 1, (3R)-1-(*tert*-butoxycarbonyl)-3-[(4-fluorobenzylthio)methyl]pyrrolidine (0.5818g,

1.79mmol) was reacted with 57-86% 3-chloroperoxybenzoic acid (0.4477g) in ethyl acetate (35ml) to give 0.5233g (86%) of the *title compound* as a colourless oil. δ_H (360MHz, $CDCl_3$) 1.45 (9H, s), 1.66 (1H, m), 2.15 (1H, m), 2.54-(1H, m), 2.63-2.71 (2H, m), 3.03 (1H, m), 3.31 (1H, m), 3.44 (1H, m), 3.65 (1H, m), 3.96 (2H, s), 7.08 (2H, t, J=8.6Hz), 7.25-7.29 (2H, m). m/e (ES+) 342 $(M+H)^+$.

2. (3R)-3-[(4-Fluorobenzylsulfinyl)methyl]pyrrolidine

Using a similar procedure to that described in Example 93, step 2, (3R)-1-(*tert*-butoxycarbonyl)-3-[(4-fluorobenzylsulfinyl)methyl]pyrrolidine (0.5149g, 1.51mmol) was reacted with trifluoroacetic acid (2ml) in dichloromethane (6ml) to give, after work up, 0.3447g (95%) of the *title compound* as a white solid, which was used without further purification. δ_H (360MHz, $CDCl_3$) 1.57 (1H, m), 2.13 (1H, m), 2.54-2.72 (4H, m), 3.05 (2H, m), 3.27 (1H, m), 3.96 (2H, m), 7.08 (2H, t, J=8.6Hz), 7.26-7.30 (2H, m).

3. (3R)-3-[(4-Fluorobenzylsulfinyl)methyl)-1-{2-(5[(1,2,4-triazol-1-yl)methyl]-1H-indol-3-yl)ethyl}pyrrolidine. Hydrogen Oxalate.

Using a similar method to that described in Example 108, step 3, 3-(2-hydroxyethyl)-5-[(1,2,4-triazol-1-yl)methyl)-1H-indole (0.1200g, 0.495mmol) was reacted with methanesulfonyl chloride (58.7µl, 0.743mmol) and triethylamine (0.138ml, 0.990mmol) in THF (3ml), then with (3R)-3-[(4-fluorobenzylsulfinyl)methyl]pyrrolidine (0.1793g, 0.743mmol) and sodium carbonate (0.1048g, 0.989mmol) in 2-propanol (12ml) to give, after purification by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 92:8:0.8), then by preparative t.l.c. (silica gel, CH_2Cl_2/MeOH/NH_3, 90:10:1), 70.1mg (30%), of the *title compound*, free base. The oxalate salt was prepared in methanol-diethyl ether: mp 72°C (softens). (Found: C, 57.68; H, 5.85; N, 11.82. $C_{25}H_{28}FN_5OS \cdot C_2H_2O_4 \cdot 0.23(C_4H_{10}O) \cdot 0.5\ H_2O$ requires: C, 57.65; H, 5.77; N, 12.04%). δ_H (360MHz, DMSO-d_6) 1.79 (1H, m), 2.25 (1H, m), 2.80 (2H, m), 2.92 (1H, m), 3.04 (3H. m), 3.35 (4H, m), 4.01 (1H, dd, J=2.9 and 12.9Hz), 4.21 (1H, dd, J=5.8 and 13.0Hz), 5.44 (2H, s), 7.07 (1H, d,

J=8.4Hz), 7.23 (1H, t, J=8.8Hz), 7.26 (1H, s), 7.34-7.41 (3H, m), 7.61 (1H, s), 7.95 (1H, s), 8.81 (1H, s), 11.03 (1H, s) among other signals. m/e (ES+) 466 $(M+H)^+$.

EXAMPLE 109

(3R)-3-[(4-Fluorobenzylsulfonyl)methyl)-1-{2-(5[(1,2,4-triazol-1-yl)methyl]-1H-indol-3-yl)ethyl}pyrrolidine. Hydrogen Oxalate.

1. (3R)-1-(*tert*-Butoxycarbonyl)-3-[(fluorobenzylsulfonyl)methyl]pyrrolidine

To a stirred solution of (3R)-1-(*tert*-butoxycarbonyl)-3-[(4-fluorobenzylthio)methyl]pyrrolidine (0.5671g, 1.74mmol) in ethyl acetate (35ml), cooled under argon in a bath at -40°C, was added portionwise 57-86% 3-chloroperoxybenzoic acid (0.8780g). The mixture was allowed to warm to +8°C over 1.5h, then stirred at this temperature for 1h. The mixture was then poured into 5% $NaHCO_3$ solution (30ml). The organic layer was separated and washed with more 5% $NaHCO_3$ solution (30ml), then brine (20ml), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 1% $MeOH/CH_2Cl_2$ and silica gel, Et_2O) to give 0.612g (98%) of the *title compound* as a colourless oil. δ_H (360MHz, $CDCl_3$) 1.45 (9H, s), 1.68 (1H, m), 2.19 (1H, m), 2.73 (1H, m), 2.90 (2H, m), 3.01 (1H, dd, J=8.2 and 11.0Hz), 3.29 (1H, m), 3.45 (1H, m), 3.69 (1H, dd, J=7.2 and 10.9Hz), 4.21 (2H, s), 7.11 (2H, t, J=8.6Hz), 7.39 (2H, m). m/e (ES+) 358 $(M+H)^+$.

2. (3R)-3-[(4-Fluorobenzylsulfonyl)methyl)pyrrolidine

Using a similar method to that described in Example 93, step 2, (3R)-1-(*tert*-butoxycarbonyl)-3-[(4-fluorobenzylsulphonyl)-methyl]pyrrolidine (0.6465g, 1.81mmol) was reacted with trifluoroacetic acid (2ml) in dichloromethane (6ml) to give, after work up, 0.4755g of the *title compound* as a white solid, which was used without further

purification. δ_H (360MHz, $CDCl_3$) 1.55 (1H, m), 2.15 (1H, m), 2.60-2.73 (2H, m), 2.90-3.00 (4H, m), 3.30 (1H, m), 4.21 (2H, s), 7.11 (2H, t, J=8.6Hz), 7.37-7.41 (2H, m).

3. (3R)-3-[(4-Fluorobenzylsulfonyl)methyl)-1-{2-(5[(1,2,4-triazol-1-yl)methyl]-1H-indol-3-yl)ethyl}pyrrolidine. Hydrogen Oxalate.

Using a similar method to that described in Example 108, step 3, 3-(2-hydroxyethyl)-5-[(1,2,4-triazol-1-yl)methyl]-1H-indole (0.1480g, 0.611mmol) was reacted with methanesulfonyl chloride (72.4µl, 0.916mmol) and triethylamine (0.170ml, 1.22mmol) in THF (5ml), then with (3R)-3-[(4-fluorobenzylsulfonyl)methyl]pyrrolidine (0.2360g, 0.917mmol) and sodium carbonate (0.1295g, 1.22mmol) in 2-propanol (14ml) to give, after purification by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 94:6:0.6), 48.7mg (17%) of the *title compound*, free base. The oxalate salt was prepared in methanol-diethyl ether: mp 79°C (softens). (Found: C, 53.86; H, 5.49; N, 10.64. $C_{25}H_{28}FN_5O_2S \cdot 1.5(C_2H_2O_4) \cdot 0.2(C_4H_{10}O) \cdot 0.6\ H_2O$ requires: C, 53.86; H, 5.37; N, 10.90%). δ_H (360MHz, DMSO-d_6) 1.81 (1H, m), 2.16 (1H, m), 2.87 (1H, m), 3.05 (2H, m), 3.30-3.42 (4H, m), 4.56 (2H, s), 5.44 (2H, s), 7.07 (1H, d, J=8.6Hz), 7.25-7.29 (3H, m), 7.35 (1H, d, J=8.3Hz), 7.45-7.49 (2H, m), 7.62 (1H, s), 7.95 (1H, s), 8.81 (1H, s), 11.04 (1H, s) among other signals. m/e (ES+) 482 $(M+H)^+$.

EXAMPLE 110

4-(4-Fluorobenzylsulfinyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl]propyl}piperidine. Hydrogen Oxalate.

1. 1-(*tert*-Butoxycarbonyl)-4-(4-fluorobenzylthio)piperidine

To a stirred solution of 4-fluorobenzyl mercaptan (23.34g, 164mmol) in DMF (150ml) under argon, cooled in a bath at -2°C, was added portionwise 60% NaH in oil (6.57g, 164mmol) over 12 minutes. The mixture was then

stirred at room temperature for 15 minutes before recooling in bath at -2°C and adding by cannular, over 13 minutes, a solution of 4-bromo-1(*tert*-butoxycarbonyl)piperidine (10.84g, 41.0mmol) in DMF (50ml). The mixture was then stirred at room temperature for 24h before partitioning between water (500ml) and diethyl ether (500ml). The aqueous layer was reextracted with more diethyl ether (500ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 10-15% EtOAc/hexane) to give 4.58g (34%) of the *title compound* as a colourless oil. δ_H (360MHz, $CDCl_3$) 1.45 (9H, s), 1.49 (2H, m), 1.86 (2H, m), 2.67 (1H, m), 2.88 (2H, m), 3.73 (2H, s), 3.92 (2H, m), 6.99 (2H, t, J=8.6Hz), 7.28 (2H, m). m/e (ES+) 326 $(M+H)^+$.

2. 1-(*tert*-Butoxycarbonyl)-4-(4-fluorobenzylsulfinyl)piperidine

Using a similar method to that described in Example 107, step 1, 1-(*tert*-butoxycarbonyl)-4-(4-fluorobenzylthio)piperidine (1.5065g, 4.63mmol) was reacted with 57-86% 3-chloroperoxybenzoic acid (1.0190g) in dichloromethane (100ml) to give 1.5287g (97%) of the *title compound* as a white solid. δ_H (250MHz, $CDCl_3$) 1.46 (9H, s), 1.64-1.82 (3H, m), 2.02 (1H, m), 2.63 (1H, m), 2.81 (2H, m), 3.88 (1H, d, J=13.2Hz), 3.98 (1H, d, J=13.2Hz), 4.21 (2H, m), 7.08 (2H, t, J=8.6Hz), 7.29 (2H, m); m/e (ES+) 683 $(2M+H)^+$, 342 $(M+H)^+$.

3. 4-(4-Fluorobenzylsulfinyl)piperidine

Using a similar method to that described in Example 108, step 2, 1-(*tert*-butoxycarbonyl)-4-(4-fluorobenzylsulfinyl)piperidine (1.524g, 4.46mmol) was reacted with 90% formic acid (15ml) to give 1.0276g (95%) of the *title compound* as a white solid. δ_H (250MHz, $CDCl_3$) 1.47 (2H, m), 1.82 (2H, m), 2.49 (2H, m), 2.69 (1H, tt, J=4.0 and 11.8Hz), 3.03 (2H, m), 3.88 (1H, d, J=13.0Hz), 4.11 (1H, d, J=13.0Hz), 7.20 (2H, t, J=8.9Hz), 7.37 (2H, m). m/e (ES+) 242 $(M+H)^+$.

4. 4-(4-Fluorobenzylsulfinyl)-1-{3-[5-(1,2,4-triazol-4-yl)-1H-indol-3-yl)propyl}piperidine. Hydrogen Oxalate.

Using a similar procedure to that described in Example 108, step 3, 3-(3-hydroxypropyl)-5-(1,2,4-triazol-4-yl)-1H-indole (0.1499g, 0.619mmol) was reacted with methanesulfonyl chloride (0.103ml, 1.30mmol) and triethylamine (0.183ml, 1.31mmol) in THF (20ml) at room temperature and then with 4-(4-fluorobenzylsulfinyl)piperidine (0.2376g, 0.985mmol) and anhydrous potassium carbonate (0.1822g, 1.32mmol) in anhydrous 2-propanol (20ml) at reflux overnight to give, after purification by flash chromatography (silica gel, CH_2Cl_2/MeOH/NH_3, 92:8:0.8) and preparative t.l.c. (silica gel, CH_2Cl_2/MeOH/NH_3, 90:10:1), 0.1159g (40%) of the *title compound* free base. The oxalate salt was prepared in ethanol-diethyl ether; mp 100°C (softens). (Found: C, 55.09, H, 5.35, N, 11.30. $C_{25}H_{28}FN_5OS \cdot 1.5(C_2H_2O_4) \cdot 0.6H_2O$ requires: C, 55.00, H, 5.31, N, 11.45%). δ_H (360MHz, DMSO-d_6) 1.90 (2H, m), 2.00-2.16 (4H, m), 2.77 (2H, t, J=7.2Hz), 2.85 (1H, m), 2.90-3.06 (4H, m), 3.96 (1H, d, J=13.1Hz), 4.17 (1H, d, J=13.1Hz), 7.21 (2H, t, J=8.8Hz), 7.31-7.34 (2H, m), 7.39 (2H, m), 7.50 (1H, d, J=8.6Hz), 7.81 (1H, d, J=1.9Hz), 9.01 (2H, s), 11.18 (1H, s) among other signals. m/e (ES+) 466 $(M+H)^+$.

EXAMPLE 111

2*S*-2-(N-Benzyl-N-methylaminomethyl)-1-[2-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)ethyl]pyrrolidine oxalate

1. Intermediate 5: 2-(5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)acetonitrile

a) 4-Methyl-5-nitro-2-(1,2,4-triazol-1-yl)pyridine

To a solution of 1,2,4-triazole (4.0g, 58mmol) in dry dimethyl formamide (20ml) was added potassium carbonate (12.0g, 87mmol) and

2-chloro-4-methyl-5-nitropyridine (10g, 58mmol) and the mixture stirred at ambient temperature under nitrogen for 24h. Ethyl acetate (500ml) and water (250ml) were added to the mixture and the resulting precipitate was collected by filtration to give the *title compound* (5.08g, 43%) as a pale brown solid. The filtrate was separated and the organic phase was washed with water (250ml) and brine (250ml), dried ($MgSO_4$) and evaporated. The residue was triturated with ethyl acetate and the precipitate collected by filtration to give the *title compound* as a brown solid (4.11g, 35%, overall yield 78%); mp 198-200°C. ^1H NMR (360MHz, $CDCl_3$) δ 2.72 (3H, s), 7.86 (1H, s), 8.07 (1H, s), 9.03 (1H, s), 9.15 (1H, s).

b) N,N-Dimethyl-2-(5-nitro-2-(1,2,4-triazol-1-yl)-pyridin-4-yl)ethenamine

To a suspension of 4-methyl-5-nitro-2-(1,2,4-triazol-1-yl)pyridine (4.1g, 20mmol) in dry dimethylformamide (30ml) was added dimethylformamide dimethyl acetal (5.9ml, 44mmol) and the mixture heated at 90°C for 20 min. The solvent was evaporated *in vacuo* using toluene as an azeotrope to give the *title compound* (5.2g, 100%) as a dark red solid; mp 225-228°C. ^1H NMR (360MHz, $CDCl_3$) δ 3.10 (6H, s), 6.13 (1H, J=13.1Hz), 7.54 (1H, J=13.1Hz), 7.81 (1H, s), 8.04 (1H, s), 8.92 (1H, s), 9.17 (1H, s).

c) 5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridine

N,N-Dimethyl-2-(5-nitro-2-(1,2,4-triazol-1-yl)pyridin-4-yl)ethenamine (8g, 31mmol) was hydrogenated over platinum oxide (1.6g) in ethanol (150ml) at 30psi of hydrogen for 1h. The catalyst was removed by filtration and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with ethyl acetate to afford an orange/brown solid. This was triturated with ether and the precipitate collected by filtration to give the title compound (2.89g, 51%) as a pink solid; mp 203-205°C., ^1H NMR (360MHz, d_6-DMSO) δ 6.67 (1H, d,

J=3.0Hz), 7.76 (1H, d, J=2.9Hz), 8.01 (1H, s), 8.23 (1H, s), 8.70 (1H, s), 9.25 (1H, s), 11.86 (1H, br s).

d) N,N-Dimethyl-[5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl]methylamine

To aqueous dimethylamine (40%, 0.35ml, 2.8mmol), was added acetic acid (1.46ml, 26mmol) at 0°C. Aqueous formaldehyde solution (38%, 0.21ml, 2.8mmol) was added and the mixture was stirred at 0°C for 5 min. 5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridine (0.5g, 2.7mmol) was added in one portion and then the mixture was allowed to warm to room temperature and then heated at 60°C for 18h. The reaction was cooled to 0°C and treated with NaOH (4M, 8ml) to basify. Water (20ml) was added, followed by dichloromethane (50ml). The solid generated was removed by filtration and the two layers of the filtrate were separated. The aqueous phase was extracted with dichloromethane (5 x 50ml) and the combined organics were dried (Na_2SO_4) and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with 10% MeOH in DCM followed by a gradient of 90:10:1 to 80:20:1, DCM/MeOH/NH_3 to afford the *title compound* (0.58g, 87%) as a colourless solid; mp 172-175°C. ^{1}H NMR (360MHz, d_6-DMSO) δ 2.16 (6H, s), 3.59 (2H, s), 7.65 (1H, s), 8.04 (1H, s), 8.22 (1H, s), 8.64 (1H, s), 9.25 (1H, s), 11.69 (1H, br s).

e) N-([5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl]methyl)-N,N,N-trimethylammonium methyl sulphate

A mixture of dimethylsulphate (0.13ml, 1.4mmol) and dry THF (5ml) was cooled to 0°C under nitrogen and N,N-dimethyl-[5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl]methylamine (0.15g, 0.62mmol) was added portionwise over a period of 5 min. The mixture was stirred at 0°C for 90 min. The resulting precipitate was collected by filtration and washed with THF to afford the title compound (0.23g, 100%) as a

colourless solid; mp 182-185°C. ^{1}H NMR (250MHz, d_6-DMSO) δ 3.06 (9H, s), 3.38 (3H, s), 4.77 (2H, s), 8.08 (1H, s), 8.30 (1H, s), 8.38 (1H, s), 8.78 (1H, s), 9.31 (1H, s), 12.40 (1H, br s).

f) 2-(5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)acetonitrile

To a solution of N-([5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl]methyl-N,N,N-trimethylammonium methylsulphate (0.56g, 1.5mmol) in water (4ml) was added a solution of potassium cyanide (0.239g, 3.7mmol) in water (2ml). This mixture was heated at 70°C for 1 h. Further potassium cyanide (80mg, 1.2mmol) was added and the mixture heated for another hour at 70°C. Further potassium cyanide (80mg, 1.2mmol) was added and the mixture heated at 70°C for 1 hour and then at 100°C for 20 min. The mixture was then cooled in ice for 30 min. The precipitate was collected by filtration and washed with water. The solid was chromatographed on silica eluting with 5% MeOH in DCM to afford the title compound (0.215g, 63%) as a colourless solid; mp 218-220°C. ^{1}H NMR (250MHz, d_6-DMSO) δ 4.19 (2H, s), 7.78 (1H, s), 8.12 (1H, s), 8.26 (1H, s), 8.71 (1H, s), 9.29 (1H, s), 11.93 (1H, br s).

2. Intermediate 6: 2*S*-2-(N-Benzyl-N-methyl)aminomethylpyrrolidine

a) 2*S*-N-*tert*-Butyloxycarbonyl-2-hydroxymethylpyrrolidine

To a solution of L-prolinol (15g, 0.15mol) in DCM (250ml) was added di-*tert*-butyl dicarbonate (36.5g, 0.163mol). The solution was stirred at ambient temperature for 18h. The solvents were evaporated *in vacuo* to give the title compound (30g, 100%) as a colourless oil. δ (250MHz, $CDCl_3$) 1.47 (9H, s), 1.57-2.10 (4H, m), 3.26-3.52 (2H, m), 3.55-3.78 (3H, m), 3.86-4.00 (1H, m).

b) 2*S*-N-*tert*-Butyloxycarbonyl-2-methylsulphonylmethylpyrrolidine

A solution of methanesulphonyl chloride (6.3g, 55mmol) in dichloromethane (25ml) was added dropwise to a solution of 2*S*-N-*tert*-butyloxycarbonyl-2-hydroxymethylpyrrolidine (10g, 50mmol) and triethylamine (5.53g, 55mmol) in dichloromethane (160ml) at -5°C. The solution was stirred at 0°C for 1h and then at ambient temperature for 17h. The mixture was diluted with dichloromethane (100ml) and washed with water (100ml) and brine (100ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give the *title compound* (13.43g, 97%) as a pale yellow gum. δ (250MHz, $CDCl_3$) 1.47 (9H, s), 1.71-2.10 (4H, m), 3.01 (3H, s), 3.28-3.46 (2H, m), 3.90-4.36 (3H, m).

c) 2*S*-N-*tert*-Butyloxycarbonyl-2-(N-benzyl-N-methyl)aminomethylpyrrolidine

A solution of 2*S*-N-*tert*-butyloxycarbonyl-2-methylsulphonylmethyl pyrrolidine (2g, 7.2mmol) and N-benzylmethylamine (4.6ml, 36mmol) in dry DMF (5ml) was stirred at ambient temperature for 2h and then heated at 100°C for 8h. The reaction mixture was partitioned between ether (50ml) and water (50ml). The organic phase was washed with brine (30ml), dried (Na_2SO_4) an evaporated *in vacuo*. The residue was chromatographed on silica eluting with EtOAc:Petrol (60/80) (1:1) to give the *title compound* (1.07g, 49%) as an orange oil. δ (250MHz, $CDCl_3$) 1.46 (9H, s), 1.55-2.04 (5H, m), 2.10-2.60 (4H, m), 3.19-3.42 (3H, m), 3.52-4.09 (2H, m), 7.18-7.40 (5H, m).

d) 2*S*-2-(N-Benzyl-N-methyl)aminomethyl)pyrrolidine

A solution of 2*S*-N-*tert*-butyloxycarbonyl-2-(N-benzyl-N-methyl)aminomethylpyrrolidine (1.07g, 3.5mmol) and trifluoroacetic acid (2ml) in dichloromethane (20ml) was stirred at room temperature for 16h, heated at reflux for 8h and then stirred at room temperature for a further 16h. The solvents were evaporated *in vacuo* and the residue was partitioned between ethyl acetate (50ml) and K_2CO_3 (saturated, 50ml).

The aqueous was extracted with ethyl acetate (3 x 25ml), dichloromethane (2 x 25ml) and butanol (2 x 25ml). The EtOAc and DCM layers were dried (Na_2SO_4) and combined with the butanol phases and evaporated. The residue was chromatographed on silica with DCM/MeOH (98:2) followed by DCM/MeOH/NH_3 (90:10:1) to afford the *title compound* (0.62g, 86%) as a pale yellow oil. δ (250MHz, $CDCl_3$) 1.38-1.50 (1H, m), 1.60-2.08 (3H, m), 2.27 (3H, s), 2.30-2.50 (2H, m), 2.77-2.87 (1H, m), 2.95-3.05 (1H, m), 3.36-3.65 (3H, m), 4.85 (1H, br s), 7.23-7.36 (5H, m).

3. 2-(5-(1,2,4-Triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)acetic acid (2*S*-2-(N-benzyl-N-methylaminomethyl)pyrrolidinyl)amide

To a suspension of Intermediate 5 (0.89g, 4.0mmol) in methanol (10ml) was added sodium hydroxide (2M, 25ml). This mixture was heated at 80°C for 16h. After cooling the mixture was neutralised (2M HCl) and the solvents evaporated. The residue was chromatographed on silica eluting with a gradient of 90:10:1 to 80:20:2, DCM/MeOH/Acetic acid followed by MeOH to afford 2-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c] pyridin-3-yl)acetic acid (3g) as a pale yellow solid. ^{1}H NMR (360MHz, d_6-DMSO) δ 3.53 (2H, s), 7.58 (1H, s), 7.98 (1H, s), 8.20 (1H, s), 8.60 (1H, s), 9.22 (1H, s), 11.68 (1H, br s). This was used without further purification in the next step.

To a suspension of 2-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)acetic acid (0.84g) in dry DMF (5ml) was added Intermediate 6 (0.262g, 1.3mmol), 1-hydroxybenzotriazole (0.174g, 1.3mmol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.247g, 1.3mmol) and triethylamine (0.18ml, 1.3mmol), and this mixture was stirred at room temperature under nitrogen for 64h. The mixture was neutralised (2M HCl) and the solvent evaporated *in vacuo*. The residue was triturated with DCM and the solid removed by filtration. The filtrate was evaporated *in vacuo* and the residue chromatographed on silica with 5% MeOH in DCM followed by a gradient of 95:5:1 to 90:10:1

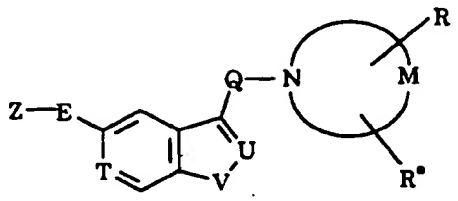
DCM/MeOH/NH_3 to afford the *title compound* (87mg) as a yellow gum. ^1H NMR (360MHz, $CDCl_3$) δ 1.54-2.70 (10H, m), 3.28-3.92 (5H, m), 4.09-4.16 and 4.34-4.44 (1H, 2xm), 7.16-7.41 (6H, m), 7.98 and 8.00 (1H, 2xs), 8.07 and 8.09 (1H, 2xs), 8.42 and 8.45 (1H, 2xs), 9.08 and 9.10 (1H, 2xs), 9.12-9.30 (1H, m).

4. 2*S*-2-(N-Benzyl-N-methylaminomethyl)-1-[2-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)ethyl]pyrrolidine oxalate

To a solution of $LiAlH_4$ in ether (1.0M, 0.6ml, 0.6mmol) and dry THF (2ml) was added a solution of 2-(5-(1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-3-yl)acetic acid (2*S*-2-(N-benzyl-N-methyl-aminomethyl)pyrrolidinyl)amide (87mg, 0.2mmol) in dry THF (3ml) dropwise at ambient temperature under nitrogen. The mixture was heated at 50°C for 1h. After cooling, water (24μL) was added, followed by sodium hydroxide (4M, 24μL), followed by water (72μL). The solid was removed by filtration and the solvent evaporated *in vacuo*. The residue was chromatographed on silica eluting with a gradient of 5 to 10% MeOH in DCM followed by 90:10:1, DCM/MeOH/NH_3 to afford a yellow gum. This was rechromatographed on silica eluting with a gradient of 98:2:1 to 95:5:1 DCM/MeOH/NH_3 to afford the free base (53mg, 63%) as a yellow gum. The free base (40mg, 0.1mmol) was dissolved in ether/MeOH (4:1, 5ml) and treated dropwise with a solution of oxalic acid (8.7mg, 0.1mmol) in ether (1ml). The precipitate formed was collected by filtration to afford the title compound (30mg) as a beige solid. mp 100°C (dec.). Found: C, 56.90; H, 6.22; N, 16.44. $C_{24}H_{28}N_7 \cdot 1.75(CO_2H)_2 \cdot 0.6(H_2O)$ requires C, 56.57; H, 5.82; N, 16.79%. ^1H NMR (360MHz, d_6-DMSO) δ 1.60-1.74 (1H, m), 1.83-2.23 (6H, m), 2.50-2.60 (1H, m), 2.88-2.98 (1H, m), 3.12-3.42 (4H, m), 3.48-3.84 (5H, m), 7.16-7.38 (5H, m), 7.65 (1H, d, J=2.3Hz), 8.08 (1H, s), 8.23 (1H, s), 8.68 (1H, s), 9.25 (1H, s), 11.85 (1H, br s).

CLAIMS:

1. A compound of formula I, or a salt or prodrug thereof:



(I)

wherein

Z represents an optionally substituted five-membered heteroaromatic ring selected from furan, thiophene, pyrrole, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiadiazole, triazole and tetrazole;

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms;

Q represents a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;

T represents nitrogen or CH;

U represents nitrogen or C-R^2;

V represents oxygen, sulphur or N-R^3;

R^2 and R^3 independently represent hydrogen or C_{1-6} alkyl;

M represents the residue of an azetidine, pyrrolidine or piperidine ring;

R represents a group of formula -W-R^1;

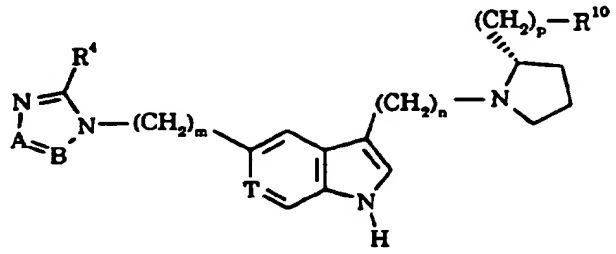
W represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally substituted in any position by a hydroxy group;

R^1 represents -OR^x, -SR^x, -SOR^x, -SO_2R^x or -NR^xR^y;

R^x and R^y independently represent hydrogen, hydrocarbon or a heterocyclic group; or R^x and R^y together represent a C_{2-6} alkylene group, which alkylene group may be optionally substituted by one or more substituents selected from C_{1-6} alkyl, aryl and hydroxy, or fused with a phenyl ring; and

R^z represents hydrogen, hydroxy, hydrocarbon or a heterocyclic group.

2. A compound as claimed in claim 1 represented by formula IIA, and salts and prodrugs thereof:



(IIA)

wherein

m is zero, 1, 2 or 3;

n is 2, 3 or 4;

p is zero, 1 or 2;

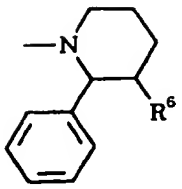
T represents nitrogen or CH;

A represents nitrogen or CH;

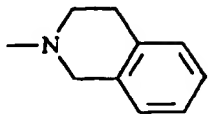
B represents nitrogen or C-R^5;

R^4 and R^5 independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl, aryl, aryl(C_{1-6})alkyl, C_{3-7} heterocycloalkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, halogen, cyano or trifluoromethyl; and

R^{10} represents -X-R^{11} or a group of formula (a) or (b):



(a)



(b)

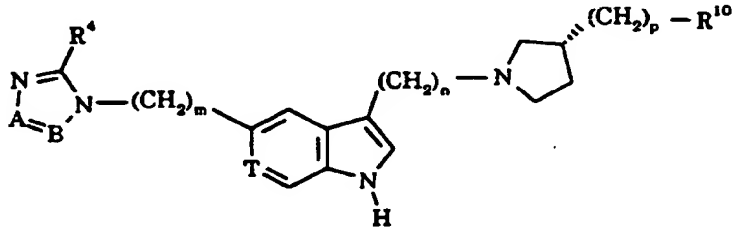
in which

R^6 represents hydrogen or hydroxy;

X represents oxygen, sulphur, -SO-, -SO_2- or N-R^{12}; and

R^{11} and R^{12} independently represent hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl(C_{1-6})alkyl, indanyl, aryl, aryl(C_{1-6})alkyl, heteroaryl or heteroaryl(C_{1-6})alkyl, any of which groups may be optionally substituted.

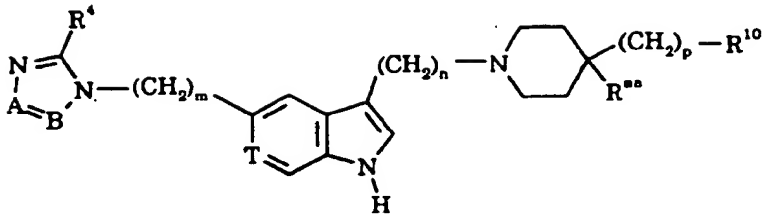
3. A compound as claimed in claim 1 represented by formula IIB, and salts and prodrugs thereof:



(IIB)

wherein m, n, p, T, A, B, R^4 and R^{10} are as defined in claim 2.

4. A compound as claimed in claim 1 represented by formula IIC, and salts and prodrugs thereof:



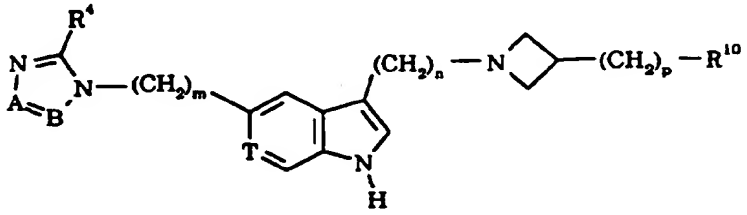
(IIC)

wherein

R^{aa} represents hydrogen, hydroxy or aryl(C_{1-6})alkyl; and

m, n, p, T, A, B, R^4 and R^{10} are as defined in claim 2.

5. A compound as claimed in claim 1 represented by formula IID, and salts and prodrugs thereof:



(IID)

wherein m, n, p, T, A, B, R^4 and R^{10} are as defined in claim 2.

6. A compound selected from:

(3*R*)-3-benzyloxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(4-methoxyphenyl)methoxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(pyridin-3-yl)methoxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-benzyloxymethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;
(2*S*)-2-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;
(3*S*)-3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;
4-(4-acetylaminophenyl)methylamino-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
4-benzylamino-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
4-(*N*-benzyl-*N*-methyl)amino-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
4-(*N*-benzyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
(2*S*)-2-(*N*-benzyl-*N*-methylaminomethyl)-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-c]pyridin-3-yl)ethyl]pyrrolidine;
and salts and prodrugs thereof.

7. A compound selected from:
4-(*N*-benzyl-*N*-methyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methyl)benzylamino]piperidine;
1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-α-(methyl)benzylamino]piperidine;
1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-α-(hydroxymethyl)benzylamino]piperidine;
1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;
1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-(1-hydroxymethyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*S*)-(2-hydroxy-1-methyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*S*,2*R*)-(2-hydroxy-1-methyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*R*)-(2-hydroxy-1-methyl-2-phenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[2-(4-acetylaminophenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methyl)benzylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-α-(methyl)benzylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*S*)-1-(4-acetylaminophenyl)ethylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-(4-acetylaminophenyl)ethylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-[(*R*)-α-(hydroxymethyl)benzyl]-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-[(*S*)-α-(hydroxymethyl)benzyl]-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(2-(4-acetylaminophenyl)ethyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(4-acetylaminobenzyl)-*N*-methylamino]methylpiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(thien-2-yl)methyl-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]methylpiperidine;

(3*S*)-3-(4-acetylaminobenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(pyridin-4-ylmethyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]azetidine;

4-benzyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

3-(*N*-benzyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]azetidine;

4-(*N*-benzyl)aminomethyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-(*N*-benzyl-*N*-methyl)aminomethyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]azetidine;

(3*S*)-3-[*N*-(*R*)-α-(methyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-(methyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(furan-3-ylmethyl)amino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(furan-2-ylmethyl)amino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

and salts and prodrugs thereof.

8. A compound selected from:

(3*S*)-3-[*N*-(*R*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-benzyl-*N*-(2-hydroxy)ethyl]aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(2-phenylethyl)amino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(2-phenylethyl)-*N*-methylamino]methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-α-dimethylbenzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-methylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*R*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*S*)-α-methylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-[*N*-(*R*)-α-(hydroxymethyl)benzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(imidazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*S*)-3-(*N*-benzyl-*N*-methyl)aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[*N*-methyl-*N*-(*S*)-α-methylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[*N*-methyl-*N*-(*R*)-α-hydroxymethylbenzyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[*N*-methyl-*N*-(*S*)-α-methylcyclohexylmethyl]aminomethyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[3-(*R*)-hydroxy-2-(*R*)-phenylpiperidin-1-yl]methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(3*R*)-3-[3-(*R*)-hydroxy-2-(*R*)-phenylpiperidin-1-yl]methyl-1-[2-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

4-hydroxy-4-(phenylsulfinyl)methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

(3*R*)-3-[2-(*R*,*S*)-phenylpiperidin-1-yl]methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

4-(3,3-dimethylpiperidin-1-yl)methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(1,2,3,4-tetrahydroisoquinolin-2-yl)methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(*N*-isobutyl-*N*-methyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-[*N*-benzyl-*N*-(2-hydroxyethyl)amino]methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-[*N*-(2,2-dimethylpropyl)-*N*-methylamino]methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-[*N*-(*R*)-α-hydroxymethylbenzyl-*N*-methylamino]methyl-4-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(2-pyridylmethyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-(2-methylphenylmethyl)aminomethyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

4-hydroxy-4-[*N*-(2-methylphenylmethyl)-*N*-methylamino]methyl-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;

3-(benzylamino)methyl-3-hydroxy-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]pyrrolidine;

3-(benzylamino)methyl-3-hydroxy-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(carbamoyl-oxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*S*)-2-hydroxy-1-phenylpropylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*R*)-2-hydroxy-1-phenylpropylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*,*S*)-1-hydroxy-2-phenylprop-2-ylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-2-hydroxy-1-(4-fluorophenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(1*R*,2*R*)-2-hydroxyindan-1-ylamino)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*,*S*)-indan-1-ylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*,*S*)-1-(4-fluorophenyl)ethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-phenylprop-2-ylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(thien-3-ylmethyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(furan-3-ylmethyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(furan-3-ylmethyl)aminopiperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*,*N*-di-(furan-3-ylmethyl)amino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(3,3-dimethylallyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(*N*-allyl-*N*-methylamino)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(indan-1-ylaminomethyl)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(*R*)-α-(hydroxymethyl)benzyl-*N*-methylaminomethyl]piperidine;

(3*R*)-3-(benzylthio)methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;

(±)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(1-benzylamino-2-hydroxyethyl)piperidine;

1-[3-(5-(1,2,4-triazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methyl)benzylamino]piperidine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(hydroxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methoxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[*N*-(*R*)-α-(methoxymethyl)benzyl-*N*-methylamino]piperidine;

1-[3-(5-(imidazol-1-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-α-(methoxymethyl)benzylamino]piperidine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-(4-fluorophenyl)-2-methoxyethylamino]piperidine;

1-[3-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)propyl]-4-[*N*-(4-fluorobenzyl)-*N*-methylamino]piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-(2-phenylpiperidin-1-yl)piperidine;

1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]-4-[(*R*)-1-(4-fluorophenyl)-2-methoxyethylamino]piperidine;

(3*R*)-3-(benzylsulfinyl)methyl-1-[2-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)ethyl]pyrrolidine;
(3*R*)-3-(4-fluorobenzylthio)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;
(3*R*)-3-(4-fluorobenzylsulfinyl)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;
(3*R*)-3-(4-fluorobenzylsulfonyl)methyl-1-[2-(5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl)ethyl]pyrrolidine;
4-(4-fluorobenzylsulfinyl)-1-[3-(5-(1,2,4-triazol-4-yl)-1*H*-indol-3-yl)propyl]piperidine;
and salts and prodrugs thereof.

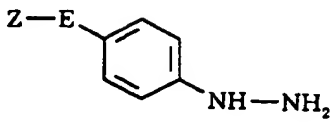
9. A pharmaceutical composition comprising a compound as claimed in any one of the preceding claims in association with a pharmaceutically acceptable carrier.

10. A compound as claimed in any one of claims 1 to 8 for use in therapy.

11. The use of a compound as claimed in any one of claims 1 to 8 for the manufacture of a medicament for the treatment and/or prevention of clinical conditions for which a subtype-selective agonist of 5-HT_{1D} receptors is indicated.

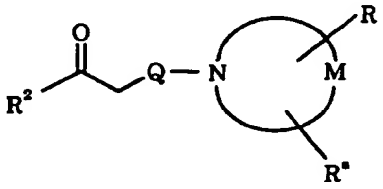
12. A process for the preparation of a compound as claimed in any one of claims 1 to 8, which comprises:

(A) reacting a compound of formula III:



(III)

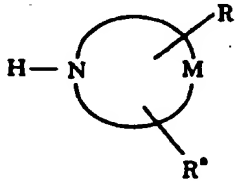
wherein Z and E are as defined in claim 1; with a compound of formula IV, or a carbonyl-protected form thereof:



(IV)

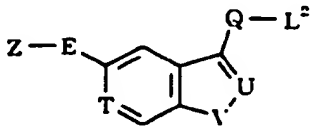
wherein R^2, Q, M, R and R^a are as defined in claim 1; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3; or

(B) reacting a compound of formula VIII:



(VII)

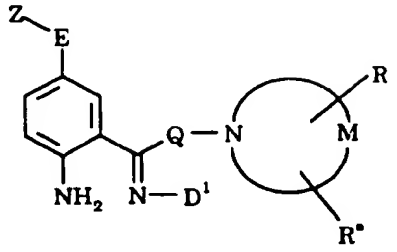
wherein M, R and R^a are as defined in claim 1; with a compound of formula VIII:



(VIII)

wherein Z, E, Q, T, U and V are as defined in claim 1, and L^2 represents a suitable leaving group; or

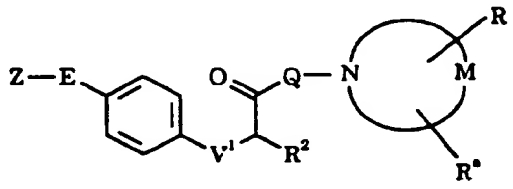
(C) cyclising a compound of formula X:



(X)

wherein Z, E, Q, M, R and R* are as defined in claim 1, and D^1 represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R^3; or

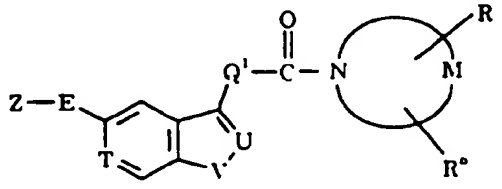
(D) cyclising a compound of formula XIII:



(XIII)

wherein Z, E, Q, R^2, M, R and R* are as defined in claim 1, and V^1 represents oxygen or sulphur; or

(E) reducing a compound of formula XVI:



(XVI)

wherein Z, E, T, U, V, M, R and R* are as defined in claim 1, and $-Q^1-CH_2-$ corresponds to the moiety Q as defined in claim 1; and

(F) subsequently, where required, converting a compound of formula I initially obtained into a further compound of formula I by conventional methods.

12. A method for the treatment and/or prevention of clinical conditions for which a subtype-selective agonist of 5-HT_{1D} receptors is indicated, which method comprises administering to a patient in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 8.

INTERNATIONAL SEARCH REPORT

Interna...al Application No
PCT/GB 95/01819

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/14 C07D401/14 C07D405/14 C07D409/14 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 02477 (MERCK SHARP & DOHME LTD.) 3 February 1994 cited in the application see claims ---	1-13
Y	EP,A,0 581 538 (MERCK SHARP & DOHME LTD.) 2 February 1994 see claims & WO,A,94 03446 cited in the application ---	1-13
A	WO,A,93 18029 (MERCK SHARP & DOHME LTD.) 16 September 1993 cited in the application see claims ---	1-13

-/--

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 1995	19. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. ..al Application No
PCT/GB 95/01819

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category `	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 497 512 (MERCK SHARP & DOHME LTD.) 5 August 1992 cited in the application see claims	1-13

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB95/01819

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ..ial Application No
PCT/GB 95/01819

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9402477	03-02-94	AU-B-	4578593	14-02-94
		CA-A-	2138649	03-02-94
		EP-A-	0651749	10-05-95
EP-A-581538	02-02-94	AU-B-	4215593	03-02-94
		WO-A-	9403446	17-02-94
		JP-A-	6184139	05-07-94
		CN-A-	1089262	13-07-94
WO-A-9318029	16-09-93	CA-A-	2129146	16-09-93
		EP-A-	0630374	28-12-94
		JP-T-	7504431	18-05-95
EP-A-497512	05-08-92	AU-B-	644939	23-12-93
		AU-B-	1068092	06-08-92
		CN-A-	1064485	16-09-92
		JP-A-	5140151	08-06-93
		NZ-A-	241394	27-04-94
		US-A-	5298520	29-03-94